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Pineal parenchymal tumour of intermediate differentiation (PPTID): Excellent response to treatment leads to an unexpected complication.

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Pineal region glioblastoma: report of two long term survivors

Dr. Pankaj Nanda ¹, Prof. Philip Kane ¹, Mr. Anil Varma ¹

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Post-operative fractionated stereotactic radiosurgery (fSRS) to the resection cavity of brain metastases – a single institution review.

Dr. Chloë May ¹, Dr. Helen Wong ¹, Dr. David Husband ¹, Dr. Aditya Shenoy ¹, Dr. Brian Haylock ¹

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Radiomic evaluation of treatment response in patients with glioblastoma: a pilot study

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Retrospective single centre review of temozolomide (TMZ) vs procarbazine, carboplatin, vincristine (PCV) chemotherapy in patients with glioblastoma (GBM) WHO grade IV at first relapse following treatment with the Stupp protocol.

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Segmentation of brain tumor in fluid-attenuated inversion recovery magnetic resonance imaging by gray-level occurrence matrix and extreme learning machine

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Stacked In-plane Histology for Quantitative MRI Assessment: Application to An infiltrative Brain Tumour Model

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Support group for newly diagnosed patients with brain tumours

Ms. Laura Mullens³, Ms. Jessica La ¹, Ms. Victoria Hurwitz ², Ms. Liz Ford ², Mr. Keyoumars Ashkan ¹, Mr. Ranj Bhangoo ¹, Mr. Richard Gullan ¹, Mr. Francesco Vergani ¹, Dr. Lucy Brazil ³, Dr. Angela Swampillai ³, Mrs. Deborah Samson ³

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Systematic review and meta-analysis: arterial apin labelling (ASL) efficiency in grading of adults glioma

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The challenges of treating a high grade glioma in a pregnant patient

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The Neurosurgical Admissions pro-forma

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Treating high-grade glioma (HGG) in the elderly: has anything changed?

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Variable RNA sequencing depth impacts gene signatures and target compound robustness – case study examining brain tumour (glioma) disease progression

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1. Johns Hopkins University, 2. Queen's University Belfast, 3. University of Bristol, 4. Belfast Trust, NHS, 5. Tampere University of Technology
A phase I expansion study of pegargiminase, cisplatin and pemetrexed in argininosuccinate synthetase 1-negative recurrent high grade gliomas (HGGs)

Oral

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**BACKGROUND:** Patients (pts) with recurrent HGGs are usually managed with alkylating chemotherapy +/- bevacizumab. However, prognosis remains poor with an overall survival (OS) of 7-9 months. Preclinically, we showed that HGGs are a target for arginine depletion with Pegargiminase (ADI-PEG20) due to epimutations of argininosuccinate synthetase (ASS1) and argininosuccinate lyase (ASL). Moreover, ADI-PEG20 disrupts pyrimidine pools in ASS1-ve HGGs, thereby impacting sensitivity to the antifolate, pemetrexed.

**METHODS:** We expanded a phase 1 trial of ADI-PEG20 with pemetrexed and cisplatin (ADIPEMCIS), which noted activity in aggressive thoracic cancers, to pts with relapsed HGGs (clinicaltrials.gov NCT02029690). Pts with ASS1-ve recurrent HGGs were enrolled (01/16 – 06/17) to receive ADI-PEG20 weekly at the maximum tolerated dose of 36 mg/m$^2$ i.m. plus PEM 500 mg/m$^2$ and CIS 75 mg/m$^2$ i.v. every 3 weeks for up to 6 cycles. Pts with disease control were allowed ADI-PEG20 maintenance. The primary endpoints were safety, tolerability and preliminary estimates of activity. Additional endpoints included pharmacodynamics, immunogenicity, OS, and ASS1/ASL epimutations.

**RESULTS:** 10/19 ASS1-ve heavily pre-treated pts were enrolled onto ADIPEMCIS therapy. Treatment was well tolerated with the majority of adverse events (AEs) being CTCAE v4.03 grade 1-2; 7 pts (70%) had at least one grade 3 or 4 AE with neutropenia (40%) and thrombocytopenia (30%). The best response was stable disease by RECIST 1.1 and partial response (n=1; 10%) by RANO criteria. The median (95% CI) OS was 6.5 (1.8, 9.7) months. Two pts are alive and one continues 16 months on ADI-PEG20 as 3rd-line therapy for a de novo IDH-wildtype glioblastoma multiforme. Epimutations in ASS1 and/or ASL were detectable in pts’ tumours consistent with prior studies.

**CONCLUSIONS:** ADIPEMCIS was well tolerated and compares favourably to historical controls in recurrent HGG. A randomised, phase II trial comparing ADIPEMCIS with alkylating drugs at first relapse is planned (ATOMIC-G).
A pilot study of the acceptance and tolerability of tumour treating fields in adult glioblastoma patients

Oral

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BACKGROUND: Tumour treating fields are a novel anticancer treatment that uses alternate electrical fields to disrupt cell division. It has been shown in a randomized controlled trial to significantly improve survival in patients with Glioblastoma. Use of the device is intensive for patients, with almost constant electrode application and battery use. The acceptability and tolerability for this new treatment is not known in a UK setting. The treatment currently costs €21,000 per month. METHODS: Three UK centres were offered support for trialing the treatment. Patients with proven MGMT unmethylated glioblastoma, had completed Stupp, had a performance score >70, and had social support (for placing the electrodes), where approached. Monthly assessments of compliance and quality of life (QOL) (ECOG BT 30), and quarterly MRIs and tolerability questionnaires were completed. RESULTS: Oncologists in one centre refused to support any use of the device, so no patients were approached in that centre. 8 patients were approached in the other two centres, 5 accepted, and 1 further patient had treatment started elsewhere. All patients tolerated the treatment, with no reduction in QOL outcomes. Patients approached were grateful to have been offered the treatment. The main reason for refusal was monthly travelling for compliance checks. The main adverse comments related to the weight of the mobile battery. One patient had skin irritation, and two patients found that the only aspect of life affected was showering. Two patients have progressed on treatment, with one having second line surgery, and both second line chemotherapy. CONCLUSIONS: Tumour treating fields is a well tolerated but intensive treatment, and acceptable to a UK population. A significant reduction in cost is required to allow routine UK use on the NHS.
Accuracy of contouring by neuro-oncologists for delivery of fractionated stereotactic radiotherapy (fSRT) and stereotactic radiosurgery (SRS) for benign intracranial conditions; what do the neuro-radiologist and neuro-surgeon add?

Oral

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Variability exists between clinical oncologists when contouring gross tumour volume (GTV) and normal tissue organs at risk (OAR) volumes. This variability is the ‘weakest link’ in the context of the highly conformal and highly accurate treatment delivery used for SRS and fSRT. In 2016-17 NHS England commissioned 17 SRS centres. The service specification mandates “treatment protocols will ensure that target definition is performed by either a sub-specialised neuro-surgeon and / or neuro-oncologist (clinical oncologist) with input from a neuro-radiologist before a treatment plan is created.” To evaluate the additional contribution by the neuro-radiologist we analysed contouring conformity for 90 patients with benign conditions treated in our centre (September 2014 – February 2018) using fSRT or SRS. GTV margins contoured by the clinical oncologist were copied and amended with the neuro-radiologist and sometimes neurosurgeon. Clinical target volumes (CTV) were added depending on the tumour type and grade, 1 mm margin was added to CTV for the planning target volume (PTV). The 90 patients included 71 meningioma, 10 pituitary adenoma, 6 craniopharyngioma, 3 other. Doses used were: 45-59.4 Gy in 30-33 fractions for fSRT and 14-16Gy for SRS. We used Eclipse TPS (v13.7) for Varian (Palo Alto, CA) Clinac iX with millennium MLC (5 mm) and Exactrac imaging system (Brainlab, Munich DE). All plans were created either using dynamic conformal arc (DCA) or VMAT RapidArc (RA) techniques with 6 MV photons and calculated using AAA (v10) on a 1 mm dose grid. Values for the final treated GTV and PTV (A) were compared with the GTV and PTV that were generated by the Clinical oncologist alone (B) will be compared using the Conformity analysis consisted of Jaccard coefficient, Dice coefficient, Geographical Miss and Discordance index as defined below. Results will be presented.
Actinomycin-D downregulates Sox-2 and reduces tumour growth in a pre-clinical model of glioblastoma

**Oral**

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**BACKGROUND:** Actinomycin-D (ACTD) is antineoplastic antibiotic and is used to treat a variety of childhood cancers, including neuroblastoma. Few studies have investigated the efficacy of ACTD in high grade glioma; however our 3D-high throughput assay system has identified ACTD to be highly cytotoxic over a panel of twelve patient-derived glioma stem-like cell lines (GSCs). Here, we validate ACTD as a potential repurposed therapeutic for glioblastoma through the use of three-dimensional GSC culture and a patient-derived xenograft (PDX) model of glioblastoma.

**METHODS:** Patient-derived GSCs were stably transduced with luciferase-expressing lentivirus to allow for reproducible *in vivo* assessment of orthotopic brain tumours by bioluminescence imaging (BLI). GSCs were treated *in vitro* with ACTD at established IC50 concentrations. Downregulation of SOX-2, a stem cell transcription factor, was investigated via western blot in cell lysates and through immunohistological assessment of murine brain tissue.

**RESULTS:** Tumour growth in a recurrent PDX orthotopic model was tracked via BLI over a period of eight weeks. Treatment with ACTD was shown to significantly reduce tumour growth in a recurrent GBM PDX model, when compared to the current standard of care, temozolomide. We also demonstrate that ACTD specifically down-regulates the expression of SOX-2 both *in vitro* and *in vivo*.

**CONCLUSION:** These findings indicate that ACTD could deplete the cancer stem-cell population within the tumour mass, ultimately leading to a delay in tumour progression.
Association between metabolic parameters from dynamic 18F-fluoromethylcholine PET, pharmacokinetic parameters from DCE-MRI, choline to creatine ratios from MRS and tissue immunohistochemistry for choline kinase alpha expression in human brain glioma.

INTRODUCTION: Proton MR spectroscopy and Choline-PET probe different aspects of choline metabolism, and quantitative dynamic MRI yields information on vascular permeability and perfusion. The relationship between these features in different grades of glioma is, however, unclear. METHOD: 14 patients with suspected primary supratentorial glioma were recruited to this study. The mean values over the whole tumour (T2-FLAIR hyperintense regions) of DCE-derived pharmacokinetic parameters were correlated with tumour to background ratio (TBR: ratio of SUV$_{\text{max}}$ in tumour to SUV$_{\text{mean}}$ in contralateral white matter for the 7-17-minute static PET images). Dynamic PET macroparameters were quantified with spectral analysis (SA) in six patients for whom metabolite data were available. Choline to creatine ratios (Cho/Cr) were extracted from 2D-CSI data over 257 MRS voxels and correlated with TBR. Tissue immunohistochemistry for choline kinase alpha expression in targeted biopsies was carried out in regions of tumour with high and low uptake on PET and Cho/Cr on MRS.

RESULTS: We observed a positive significant correlation between DCE-MRI derived parameters and parameters obtained through SA of the dynamic choline-PET data as well as TBR. We also observed a positive significant correlation between MRS Cho/Cr and TBR, although this was weak when excluding WHO Grade IV tumours. We did not observe a strong correlation between choline markers on imaging and choline kinase alpha expression.

CONCLUSION: The correlation between both DCE and MRS parameters with TBR indicates that a number of biological features affect the uptake of the PET tracer. DCE-MRI provides complimentary information to blood volume and permeability that may augment interpretation of PET data; and help address questions such as the degree to which tracer uptake is dominated by blood brain barrier permeability rather than metabolic activity. Choline imaging with PET and MRS may reflect metabolic processes that are not simply related to choline kinase alpha expression.

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Bridging the gap – Benefits of neurosurgical tissue for pre-clinical research

Oral

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The use of primary human neural tissue for research provides an invaluable insight into human neural function that cannot be achieved in any other way. Despite this it is successfully collected and used in only a small minority of units. We have established a collaboration between the Wessex Neurological Centre and the University of Southampton that allows us to study using human tissue resected during neurosurgery, and have used this tissue for over a decade. Tissue is most commonly collected from oncological, epilepsy and vascular operations. Here we share our experiences of the practicalities of working with live human glioma tissue and try to provide some insights for practicing neuro-oncology surgeons.

We discuss the ethical considerations and practical difficulties of the co-ordination of the clinical and academic teams, and challenge of optimization of the tissue for the research. We will present the mechanisms in place to optimize the study of human neural tissue.

We will review the progression from resection of tissue from glioma surgery to epilepsy surgery to any neurosurgical procedure in which the normal brain is resected and tissue discarded. We discuss the different models that can be used and the application locally to glioma stem cells, pathways activated in TBI, tissue damage from haemoglobin, the electrophysiology of the normal brain and with age and the inflammatory response of microglia.

We will present examples of the value of human tissue studies. Firstly we will show the importance of primary glioma tissue compared to established glioma cell lines. Secondly, we will demonstrate some electrophysiological differences between humans and rodent that could only be investigated through the use of live human tissue obtained at operation. We will also demonstrate how we have moved to streamline tissue collection and propose a move to establish a national framework for such experiments.
Characterization of radiotherapy-induced cerebral microbleeds with ultra-high field MRI: experience in young and adult brain tumour population

Oral

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MOTIVATION: In the treatment of brain tumours, radiation therapy (RT) is associated with long-term effects including vascular injury, changes in white matter, and cognitive decline. Vascular injury typically manifests as size-varying hemosiderin deposits in the brain called cerebral microbleeds (CMBs) which can be detected with susceptibility-weighted imaging (SWI) as early as 8 months following treatment. Similar forms of vascular injury have been related to the cognitive impairments experienced by other patient populations (e.g. stroke, vascular dementia); preliminary findings suggest a similar relationship for RT-induced CMBs, though their clinical relevance remains unclear. Further characterization of RT-induced CMBs in relation to cognition, treatment and clinical parameters is thus needed to develop a more thorough understanding of the impact of CMBs on patients with brain tumours, with the ultimate goal of mitigating CMB development and associated long-term effects without sacrificing treatment efficacy. METHODS: Ultra-high field MRI and SWI were used to detect CMBs with high sensitivity in patients treated with RT for an adult (focal) or pediatric (whole-brain) brain tumour. For the adult patients, predictors of CMB development were identified, and evolutionary changes in CMB burden were characterized across serial imaging data. Neurocognitive testing was performed for the pediatric patients and the distribution of CMBs was evaluated; global and local CMB burden were related to global and region-specific measures of cognitive function. RESULTS: Total CMB burden increased with time since RT, though individual CMBs decreased in size overtime. Risk factors for CMB development in adults included multiple surgical resections, tumour type (and subsequent RT regimen), and tumour location. Majority of CMBs were in the white matter, occipital, temporal, and frontal lobes. Increased presence of CMBs in the frontal lobe was associated with worse performance on tasks measuring execution function in children.
Clinically deliverable Optune and Deep Brain Stimulator generated electrical fields have variable efficacy on different types of brain tumour

Oral

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INTRODUCTION
Phase III trials of Tumour Treating Fields (TTFields) (Optune) have shown potentially positive results in both primary and recurrent adult Glioblastoma multiforme (GBM) patients. These results have given credence to electromagnetic fields, presenting a new treatment paradigm for brain tumour patients. Here we present investigations into repurposing deep brain stimulation (DBS) electrodes as a novel delivery method of therapeutic electric fields to high grade brain tumours and compare to TTFields treated cell lines.

METHODS
Medtronic DBS electrodes were inserted into cell culture flasks and delivered electric fields over a range of frequencies and intensities to a panel of GBM, Medulloblastoma and Ependymoma cell lines. Inovitro is the laboratory based TTFields delivery system. Inovitro was used to deliver TTFields over a range of clinically relevant frequencies (100-400kHz) to a panel of paediatric GBM, Medulloblastoma and Ependymoma cell lines. Differences in the effects of both treatments on cell viability, cell cycling, long-term effects of treatment, as well as genome-wide expression were analysed.

RESULTS
Both DBS electric fields and TTFields negatively affect cell proliferation and viability of brain tumour cell lines. The magnitude of these effects were dependent upon frequency and intensity. Cells treated with either modality were re-seeded and growth rates were compared to non-treated cells. The treated cells experienced significantly slower growth rates following treatment. Cell cycle analysis revealed that DBS treated cells have significant levels of G₀ phase accumulation relative to control flasks, while TTFields treated cells demonstrated greater levels of G₂M phase accumulation across all panels of cell lines tested. The effects of electrotreatment on gene expression will be discussed.

CONCLUSIONS
Both treatment modalities have demonstrated efficacy against our array of brain tumour cell lines. The treatments likely have differing mechanisms of action at the cellular level and this is reflected in the differences that have been observed.
Day-case brain tumour biopsy: our experience over eight years

OBJECTIVES
Day-case brain tumour biopsy is an established practice in only a limited number of UK neurosurgical centres. The reluctance to adopt this protocol may be due to the lack of published evidence on its safety. We present our experience following 8 years practice.

METHODS
All patients undergoing brain tumour biopsy between November 2009-2017 were included. Subjects were identified through hospital operations database and their electronic case notes.

RESULTS
447 biopsies were performed over 8 years with 160 intended as day-case and 135 actual day-case procedures, revealing a failure rate of 15.6% (25). Mean age was 58 years. Pathology included low grade tumours (26), high grade tumours (95), lymphoma (21), metastases (6) and non-tumours (12). Locations were broadly categorised as frontal (69), parietal (40), temporal (35), occipital (3) or posterior fossa (13). Causes for failed day-cases included post-operative haematoma, delayed imaging and new neurological deficit. Mortality rate was 0%. Re-admission rate was 3% due to seizures (3) and wound infection (1).

CONCLUSION
Close surveillance post-operatively permits for prompt delivery of care together with an enhanced patient experience. As demonstrated and consistent with other centres' experience, this is a safe and effective technique. Day-case surgery helps meet the modern demands of the NHS by improving patient flow and relieving bed pressures provided a bespoke day-case pathway exists.
Diffusion kurtosis imaging identifies the IDH mutation status of gliomas

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BACKGROUND: Since the 2016 WHO classification, the mutation status of the encoding gene of Isocitrate-dehydrogenase enzyme (IDH) is an important element in the integrated diagnosis of gliomas. Diffusion Kurtosis imaging (DKI) has been used to assess the microstructure of brain tissue as well as gliomas by quantifying the water molecules’ non-Gaussian distribution. We therefore hypothesize that DKI can determine the IDH status of gliomas. MATERIALS / METHODS: 20 patients (F/M: 12/8, mean age: 39±14.6 years) with histopathologically proven gliomas were included in this prospective study. Diffusion images were obtained on a 3T system with 10/30/60 diffusion gradient directions with b-value of 300-2500 sec/mm². Kurtosis analysis was performed using the Diffusional Kurtosis Estimator software, and segmentation was manually drawn on the co-registered FLAIR-DWI images. The mean value of the “mean kurtosis (MK)” and “mean diffusivity (MD)” were extracted from the solid tumour component and from the contralateral normal-appearing white matter. We then correlated MK and MD with the 2016 CNS WHO tumor grades using statistical software STATA, V15. RESULTS: 7 patients had IDH-wild type (wt) gliomas and 13 IDH-mutant gliomas. Normalized MK (MKn) significantly differed between IDH-mutant and IDH-wt gliomas (p=0.04), while MDn didn’t reach the statistical significance level (p=0.059). In those patients with a lack of 1p/19q co-deletion all MKn, MK, MDn, MD significantly differed (p<0.007). CONCLUSION: DKI enables the differentiation of gliomas according to the WHO 2016 integrated diagnosis. Further studies with a larger patients’ number are required to confirm these findings.
Exploring alignment-free sequence comparison methods to elucidate patterns of evolution and heterogeneity in longitudinal glioma patient cohorts

Oral

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Longitudinal glioma patient samples can reveal critical information relating to gliomagenesis, tumour evolution and therapy resistance. Previous studies examining tumour heterogeneity and evolution in these cohorts have focused solely on the limited information retained after applying stringent alignment and variant calling pipelines. Here, we propose the use of alignment-free methods to obtain an unsupervised view of the relationships between longitudinal tumour samples. Alignment-free (AF) sequence comparison is a novel methodology that has been heavily implemented in protein sequencing comparison and assessing evolutionary relationships between organisms but has not yet been applied to cancer research. Unsupervised AF methods can result in shorter computational times and may offer wider information for studying tumour heterogeneity and evolution in cancer research. In this study, we have identified a cohort of longitudinal glioma samples (Johnson et al.) for which we have whole exome-sequencing for germline, multiple spatial samples from an initial grade II glioma and spatial samples from a subsequent recurrent tumour for each patient. We developed an AF software to produce unrooted neighbour-joining trees for each patient, for which a matched least-square minimum-evolution tree produced from non-synonymous, somatic SNPs present in each of the samples is available from the original publication. Results demonstrate clear similarities when comparing the results from AF analysis to the trees produced using alignment-based approaches, however, clear and possibly fundamental differences were identified. These may be a result of the compounded effect of unassessed structural variants, larger indels or passenger synonymous variants which are also contributing to the tumours mutational landscape and therefore effecting the evolutionary pathway of gliomas. We hypothesise that this presents an opportunity to identify early and late events in evolution as well as highlight potential therapy-resistant subclones of the initial tumour which then give rise to a subsequent recurrent tumour.
First UK experience with navigated transcranial magnetic stimulation in pre-surgical mapping

**Oral**

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**OBJECTIVES:** Surgery for lesions in eloquent brain areas is challenging due to the underlying risk of causing permanent neurological deficits. To date, Direct Cortical Stimulation (DCS) and intra-operative neuro-monitoring (IOM) represent the gold standard in minimising such risk. Recently, Transcranial Magnetic Stimulation (TMS) has emerged as a mapping tool that assists in optimising surgical planning. The aim of this study is to validate our TMS findings against DCS.  

**METHODS:** Retrospective single-centre analysis of 35 adult patients with TMS, DCS and IOM for space occupying lesion (SOL) at King's College Hospital from February 2017 to February 2018. Patients with arteriovenous malformation were excluded from analysis. We collected data on patient demographics, tumour entity/location, extent of resection (EoR), change of surgical strategy, neurological outcome, and correlated TMS with DCS/IOM.  

**RESULTS:** 24/35 patients (68.6%) had pre-operative motor mapping and 11/35 (31.4%) were mapped for language. Histopathology demonstrated a glioma in 85.7% of patients (high grade n=24; low grade n=6) and metastasis (n=2), cavernoma (n=1) and other cases (n=2). TMS resulted in a change of surgical strategy in 34.3% (craniotomy size n=7; surgical pathway n=3; EoR n=1; surgical indication n=1). Sensitivity of TMS for language was 70.6% with a positive predictive value of 60.0% (n=9). TMS motor mapping correlated with DCS/IOM in all cases with snapshot hotspot conformity of 100% (n=5). A total of 12 patients had a new transient neurological deficit which resolved/significantly improved except for one case (expressive dysphasia).  

**CONCLUSIONS:** TMS is a non-invasive, safe and effective adjunct in surgery planning in eloquent brain areas. It is reliable in predicting M1/motor mapping and shows promising results for language mapping. Larger randomised controlled trials are needed to validate these findings.
INTRODUCTION: Gross total resection (GTR), defined as complete resection of enhancing tumour on post-operative MRI, increases progression free survival (PFS) in patients with glioblastoma. We have extended the concept of functionally guided supramaximal resection (SMR) where the aim of surgery is to resect up to 2 cm beyond the enhancing tumour in all directions, limited only by functional boundaries. Boundaries are identified by pre-operative diffusion tensor imaging (DTI) scans, to estimate white matter fibre tract location, and awake craniotomy with cortical and subcortical stimulation. METHODS: Prospective non-randomised functionally guided surgical resection was undertaken in all IDH-wildtype glioblastomas undergoing primary surgical resection by the senior author between 2012-2017. Based on post-operative MRI scans, data on extent of tumour resection were analysed calculating tumour, brain and post resection volumes. Patients were then categorised into three different extent of resection groups: subtotal resection (STR), GTR, and SMR. All patients underwent post-operative radiotherapy and chemotherapy as per the Stupp protocol and were followed up with 3-monthly MRI scans. RESULTS: 69 cases of IDH-wildtype glioblastoma underwent resection within the timeframe. Survival data are currently available for 45 cases. The outcome measure is PFS, where progression is defined as recurrence of tumour. For actual treatment received, median PFS was 43.9 months (95% CI, 22.8-89.8 months) in the SMR group, 29.3 months (95% CI, 7.4-72.3 months) in GTR group and 13.3 months (95% CI, 10.3-27.6 months) in the STR group. The Kaplan-Meier survival curves of the three groups are clearly separated with no crossing. The logrank test indicates there is a significant difference (P value = 0.0003) between the survival curves of the three groups. There was no difference in the incidence of post-operative neurological deficit between the three groups. CONCLUSION: Supramaximal resection provides a significant increase in PFS compared to the current accepted standard of GTR.
Genomic profiling of primary and matched recurrent glioblastoma tumours reveals that the mutational landscape includes clinically actionable variation

Oral

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Glioblastomas account for 90% of adult brain tumours and patient survival remains low. Understanding genetic alterations in subtypes could improve therapeutic intervention. Tumours from 41 patients, 8 with matched recurrent glioblastomas were genomically profiled for 130 neuro-oncology genes using a diagnostic panel. Single nucleotide variants (SNVs), copy number variations (CNVs) and potentially clinically actionable mutations were assessed for IDH-wildtype (n=38) and IDH-mutant glioblastomas (n=3). Mutational landscape revealed discrete differences and similarities between subtypes. TSC2, MSH6, TP53, CREBBP and IDH1 were co-mutated and putatively pathogenic in both subtypes, suggesting they are driver mutations. Recurrent tumours were not hypermutated and matched analysis revealed inter-tumour heterogeneity. **IDH-wildtype:** SNVs (145) impacted RTK/Ras/PI(3)K (82%), p53 (63%), WNT (58%), SHH (13%), NOTCH (11%), Rb (5%) and G-protein (8%) pathways. SNV burden was a predictor of overall survival \( P = 0.003 \) but no pathway was individually responsible. SNVs (40) in BRAF, DAXX, EGFR, FGFR2, JAK2, MYB, PIK3CA, PIK3R1, PTEN, ATM, BRCA1, CHEK2, PPM1D, PTCH1 and SMO were also putatively pathogenic. Many initial tumours had BRCA1/2 (21;18%) variants, including confirmed somatic mutations in haemangioblastoma. Survival analysis suggested GNAS variation was prognostic \( P<0.001 \). Recurrent tumours had fewer pathways (RTK/Ras/PI(3)K, p53, WNT, G-protein) impacted by genetic alterations. Possible resistance signatures included a private mutation in PIK3C2G and CNV gains (BRCA2, GNAS, EGFR) and losses (TERT, SMARCA4). Recurrent tumours (57%;4/7) harboured potentially actionable variation in PTEN, BRCA1, BRCA2, ATR and EGFR. Combination therapies with erlotinib, everolimus or dasatinib, olaparib, ATR inhibitors and EGFR-targeting antibodies, vaccines or TK inhibitors could provide therapeutic intervention. **IDH-mutant:** SNVs (15) impacted RTK/Ras/PI(3)K (66%), p53 (100%) and WNT pathways (33%). SNVs were also putatively pathogenic in KLK1 exclusively in this subtype. The recurrent tumour had fewer pathways (p53, WNT, G-protein) impacted by genetic alterations and a private mutation in TCF4. Potentially actionable variation in ATR could be targeted using inhibitors. In conclusion, TCGA-GBM and GDC datasets corroborated results confirming the clinical significance of findings. Combination therapies targeting subtype clinically actionable mutations may hold the best promise for patient oncological management.
**Gliomas genetic markers and preferential supratentorial brain locations**

**Oral**

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Introduction
Gliomas are associated with preferential locations in secondary functional areas. We examine our data to see if there is a genetic difference between the gliomas in different supratentorial locations using \( IDH-1 \), \( MGMT \) methylation and \( 1p19q \) co-deletion status.

Methods
WHO Grade II and III glioma patients with histology were included retrospectively from the MDT database from 2013 – 2017. Glioma location was determined by the MRI report. In cases where the glioma expanded beyond one lobe, consensus was obtained between the authors to determine where the majority of the tumour bulk was located. \( IDH-1 \), \( MGMT \) methylation and \( 1p19q \) co-deletion status were obtained from the histopathology report. \( \chi^2 \)-test with Bonferroni correction was used to compare the actual and expected numbers observed.

Results
191 gliomas were included. There were 55 astrocytomas Grade II, 81 astrocytomas Grade III, 24 oligodendrogliomas Grade II, 29 oligodendrogliomas Grade III and 2 anaplastic pleomorphic xanthoastrocytomas. There were 74 frontal, 25 insular, 64 temporal, 20 parietal and 8 basal ganglia tumours. 64.1% of the gliomas were \( IDH-1 \) mutated. However, 82.4% in the frontal lobe, 70.8% in the insula, 46.2% in the temporal lobe, 60.0% in the parietal lobe and 14.3% in the basal ganglia regions were \( IDH-1 \) mutated (\( p < 0.001 \)). 57.3% of the gliomas were \( MGMT \) methylated. However, 64.9% in the frontal lobe, 62.5% in the insula, 50.8% in the temporal lobe, 60.0% in the parietal lobe and 42.9% in the basal ganglia regions were \( MGMT \) methylated (\( p < 0.001 \)). 31.3% of the gliomas were \( 1p19q \) co-deleted. However, 43.2% in the frontal lobe, 29.2% in the insula, 23.1% in the temporal lobe, 25% in the parietal lobe and none in the basal ganglia were \( 1p19q \) co-deleted (\( p < 0.001 \)).

Conclusion
Our data suggest gliomas in different supratentorial locations have genetic differences based on the three genetic markers.
How should we support patients with primary brain tumours who elect to take Cannabinoids?

Introduction: Primary brain tumours account for 3% of new cancer cases (2015) but account disproportionately in terms of mortality and morbidity. With radical treatment prognosis is variable; ranging from 80% survival for 5 years or more for benign meningiomas to a dismal 5% for Glioblastoma multiforme (GBM). Understandably, increasing numbers of cancer patients are seeking Complimentary and Alternative Medicine (CAM) to improve prognosis and alleviate treatment related toxicities. There is legitimate CAM research in the UK. Yet it is challenging for vulnerable patients to disentangle legitimate researchers from dubious ones. These patients are open to manipulation and abuse via unsolicited sources offering a magical ‘cure’. It is also challenging to support patients through treatment when they may be self-medicating without their treating team being aware of the details, and possible interactions. We propose to investigate whether there is a need for specialist support for this patient population. Method: Questionnaires were distributed across 3 Neuro oncology clinics over one week (N=51). These were completed anonymously to encourage honest responses. 30 patients were on active surveillance and 21 patients were on active treatment (either radiotherapy or chemotherapy). Results: A significant number of patients were already taking some form of CAM such as turmeric, or were interested in speaking to a CAM Specialist regarding it. Of particular interest was the use of Cannabinoids (CBD) which are being explored in pre-clinical and clinical trials in brain tumours. Conclusion: We are seeing an increase in the use of CBD use amongst our patient groups who were surveyed. This survey has given us insight into our patient population and guides us on how we can best support them. We are continuing to collect questionnaires and full evaluation will be presented.
Human glioblastoma genesis mechanism from subventricular zone: Firework pattern glioblastoma genesis

Oral

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Identifying the cell of origin that harbors mutations driving GBM could provide a fundamental basis for understanding disease developing novel treatments. Given that the accumulation of somatic mutations is implicated in gliomagenesis, studies have suggested that neural stem cells (NSCs), with their self-renewal and proliferative capacities, in the subventricular zone (SVZ) of the adult human brain may be the cells from which GBM originates. However, there is a lack of direct genetic evidence thereof in human GBM patients. Here, we describe direct molecular genetic evidence from patient brain tissue and genome edited mouse models that show astrocyte-like NSCs in the SVZ to be the cell of origin that harbors the driver mutations of human GBM. First, we performed deep sequencing of triple-matched tissues, consisting of i) radiologically and pathologically normal SVZs away from the tumor mass, ii) the tumor, and iii) normal cortical tissue (or blood), from 17 patients with primary GBM (isocitrate dehydrogenase-wild type) or other types of brain tumors. In doing so, we found that normal SVZ tissue away from the tumor in 46.2% of primary GBM patients contained low-level GBM driver mutations (down to ~1% of the mutational burden; TP53, PTEN, EGFR, PDGRF or TERT variations) that were observed at high levels in their matching tumors. Moreover, via single cell sequencing and laser microdissection analysis of patient’s brain tissues and genome editing of a mouse model (CRISPR-Cas9 system), we discovered that astrocyte-like NSCs (the astrocyte ribbon area) carrying driver mutations (TP53, PTEN, EGFR) migrate from the SVZ and lead to the development of high-grade gliomas in distant brain regions through aberrant growth. Altogether, our results highlight NSCs in human SVZ as the cell of origin that harbors the driver mutations of GBM. This GBM genesis from SVZ looks like the firework pattern.
Intraoperative Raman spectroscopy identifies key mutations in human glioma: a new platform for Precision Medicine

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Human glioma can be a devastating disease with at best a median survival of only 14 months in high grade tumors. Diagnosis of these tumors increasingly relies on genetic testing of tumor tissue for IDH, ATRX and MGMT status which can take many weeks during which treatment can not be started. We describe the application of intraoperative Raman spectroscopy for the instant, label-free and non-destructive detection of key driver mutations in human glioma in an effort to shorten the time to diagnosis and help improve the detection of tumor tissue during surgery.

This study involved a prospective series of patients undergoing tumor resection through an open surgical technique (standard craniotomy). At various stages during the operation Raman analysis of tissue was performed using the sterile hand held Raman probe attached 5mm from the tip of a navigation probe positioned over the brain tissue being analysed. All biopsies were submitted and processed for genetic analysis for IDH mutation and PCR assay for MGMT promotor methylation. Data was analysed using PCA-LDA and PLS-DA to built predictive models.

Results: Using our in vivo Raman system we collected 471 Raman spectra from 17 patients undergoing brain surgery for a range of WHO grade 2-4 gliomas. The predictive models achieved 98% accuracy for identifying MGMT methylation and 94-96% accuracy for identifying ATRX and IDH mutation in vivo. Peak analysis revealed characteristic peaks for each mutation type.

Raman spectroscopy is capable of the in vivo detection of key mutations in human glioma. This can drastically shorten time to diagnosis and first treatment. It also allows the identification of good and poor prognostic groups of patients immediately at surgery. Through stratifying patients into key molecular groups for targeted therapies intraoperative Raman spectroscopy is a promising new platform for precision medicine in Neurosurgery.
Is dynamic susceptibility contrast perfusion-weighted MRI reliable in the estimation of IDH mutation in gliomas?

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BACKGROUND & PURPOSE: The presence of mutation in the encoding gene of isocitrate-dehydrogenase (IDH) enzyme has been defined as a molecular biomarker by World Health Organisation (WHO) in 2016 in the diagnosis and differentiation of gliomas. MRI techniques have been widely used in the radiological evaluation of gliomas. Among advanced MRI techniques, Dynamic Susceptibility Contrast Perfusion-Weighted Imaging (DSC-PWI) appears as a recently established technique for histopathological WHO grading of gliomas. In this study, we aimed to investigate whether DSC-PWI, enhanced by texture analysis and machine learning, can stratify gliomas according to their IDH mutation status.

MATERIAL & METHODS: 208 patients (F/M: 84/119, median age: 47 [range: 21-81 year]) from a multicenter setting, who have been immunohistopathologically diagnosed with gliomas (IDH positive/negative: 98/105) were prospectively included in our study. The raw data from DSC-PWI was processed on a dedicated workstation to create leakage-corrected relative cerebral blood volume (rCBV) maps. Tumours were manually segmented and registered to rCBV maps. rCBV maps were used to generate distribution and rotational invariant Haralick texture features over the tumour mask. The predictive power of the extracted features in differentiating between IDH status was assessed in a 2-fold cross-validation setting of 1000 iterations using support vector machine and multinomial ordinal regression, respectively.

RESULTS: In the differentiation of IDH-mutant tumours from wild-type ones, overall sensitivity and specificity rates for the rCBV values were 68% and 81%, respectively. Nine of the ten classical histogram statistics and twelve texture features appeared significantly different across mutation status (p<0.05) when using a non-parametric Wilcoxon test.

CONCLUSION: Preliminary results are promising in the differentiation of gliomas with DSC-PWI on the basis of IDH mutation status, especially regarding the high specificity rates obtained using features from rCBV data.
L1 cell adhesion molecule (L1CAM) and phosphorylated fibroblast growth factor receptor 1 (pFGFR1) expression positively correlates with neurological malignancies

Oral

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INTRODUCTION. Gliomas are intrinsic brain tumours characterised by their highly invasive, malignant and aggressive nature. Persistently poor prognoses highlight the urgent clinical need to identify novel approaches and therapeutic targets to improve glioma management. Recently we reported a correlation of fibroblast growth factor receptor 1 (FGFR1) expression with malignancy, tumour grade and location in paediatric gliomas. There is evidence that the L1 cell adhesion molecule (L1CAM) potentiates FGFR1 signalling. L1CAM is a transmembrane glycoprotein associated with poor clinical outcomes in various cancers promoting cell motility. Here, following our initial studies on FGFR1, we investigated FGFR1 in its activated phosphorylated form (pFGFR1) as well as L1CAM expression in our cohort and association with various clinicopathological parameters. METHODS. A commercially available tissue microarray (CNS2081, US Biomax) was stained for pFGFR1 and L1CAM expression and data was scored using manual and digital assessment (QuPath). Scores were separately dichotomised into low and high L1CAM and pFGFR1 expression using the median value in SPSS. A two-sided Pearson’s chi squared statistical test was performed using GraphPad Prism where p<0.05 was considered statistically significant. RESULTS. There was higher L1CAM expression in malignant tumours compared to benign tumours (p<0.05). There was higher L1CAM expression in tumours located in the cerebellum compared to the cerebrum (p<0.05). Both L1CAM and pFGFR1 expression was predominantly localised to the cytoplasm. DISCUSSION. Our results suggest that L1CAM expression is associated with malignancy. Most high-grade astrocytomas exhibited pFGFR1 cytoplasmic expression suggesting that the FGFR1 pathway is activated, which is known to be associated with cell migration and aggressive tumours. L1CAM expression was found in all tumours which suggests a role in glioma tumourigenesis. Further research on pFGFR1 and L1CAM interaction is warranted in a larger clinical cohort. pFGFR1 and L1CAM may be potentially useful biomarkers and good candidates for therapeutic intervention.
Current practice in re-irradiation (reRT) of patients with previously treated Glioblastoma (GBM) has generally been limited to small volume reRT often with stereotactic procedures. Less evidence exists for the safety, toxicity and outcomes of patients who undergo large volume reRT. This study investigates outcomes of large volume reRT in patients with recurrent refractory GBM.

Methods: Patients with GBM managed with radiation therapy were entered into a prospective ethics approved database. Patients receiving fractionated reRT from 2009-2017 were identified. Potential prognostic data were analysed for the primary endpoint of overall survival (OS) duration post reRT, such as tumour type, tumour site, age, time from diagnosis, ECOG status, MRC Neurological Scale, PTV volume, and use of bevacizumab (BEV). Kaplan Meier survival was calculated and differences between groups assessed by log-rank and Cox regression analyses.

Results: Seventy-two patients were managed with ReRT, including 51 patients with GBM. Median PTV was 117.4cm³; 92% received 35-40Gy in 15 fractions; and 80% patients received concurrent BEV and 88% post-reRT BEV. Only one episode of radiation necrosis occurred, and was in a patient with no concurrent BEV. Median OS post reRT of the 51 patients was 7 months (95% CI: 6.2-7.8). ECOG 0-1 had a median OS of 9 months (95% CI: 8.1-9.9) compared with 6 months for ECOG 2-3 (95% CI: 4.4-7.6; p=0.05). Time from diagnosis (p<0.01) was associated with improved survival but not age (p=0.16); MRC scale (p=0.19); PTV volume (p=0.62) or tumour site (p=0.72). Concurrent or post-reRT BEV was not associated with OS (p=0.57; noting that 88% received BEV and the median OS was 7 months versus 4 months with no BEV).

Conclusion: Large volume reRT with BEV produces a meaningful survival in patients with GBM, especially in patients with good performance status. It should be considered as a late salvage therapy in chemorefractory disease.
Lineage specified neural precursor cells as cell of origin of glioblastoma

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Glioblastoma multiforme (GBM) is the most prevalent adult brain tumour, with a median survival at diagnosis of 12-15 months, and is a highly heterogeneous tumour, both on the intertumoral and intratumoral level. This intertumoral heterogeneity is demonstrated by the different subtypes of GBM; with some associated with a “Proneural” transcriptional program, characterised by upregulation of oligodendrocyte developmental genes. Intratumoral heterogeneity is caused by glioblastoma initiating cells (GICs), which can give rise to different subpopulations of tumour cells with different biological properties. Here, we aim to investigate the evolutionary link between neural progenitor cells of different lineages and GBM of different molecular subgroups. We have genetically and epigenetically compared GICs with iPSC-derived syngeneic neural stem cells (iNSCs), to elucidate GICs similarities with healthy NSCs and what genetic or epigenetic markers distinguish GICs. We have generated oligodendrocyte precursor cells (iOPCs) and astrocyte precursor cells (iAPCs) by applying differentiation protocols to our iNSC lines. After characterisation of these progenitor cells we have performed RNAseq and DNA methylation array to study the relationships of these progenitors with GICs isolated from various GBM subgroups. iOPCs derived via differentiation of iNSCs, displayed OPC characteristics such as expression of OLIG2 and PDGFR-alpha. Further, iAPCs derived from iNSCs, displayed astrocytic characteristics including CD44 and GFAP expression. Genome wide transcriptomic and DNA methylation analysis can be performed on these progenitors after enrichment for specific markers by means of flow cytometry and the datasets can be computationally compared to GICs and NSC. In conclusion, neural progenitors (iOPCs and iAPCs) can be generated from iPSC-derived iNSCs and they are suitable for transcriptomic and epigenomic comparisons with GICs.
Patients diagnosed with a low grade glioma (LGG) are unique in terms of the uncertainty they experience with the disease, its prognosis and the different treatment approaches. In recognition of these needs, the low-grade glioma clinic aims to provide an individualized approach provided by a specialised multidisciplinary team which includes neuro-surgeons, neuro-psychologist, neurologist, speech therapist and clinical nurse specialist that is able to plan the patient's treatment pathway. The nature of the clinic is to allow for longer consultations tailored to patients' need in recognition of difficult treatment decisions considering the high psychological burden they may have in patients' lives. To maximise time and potentiate the care provided by this specialised team, the clinic is divided into two group of patients: those who require physical assessment or treatment decisions attend in person and those in regular follow-up who do not attend but a proper feedback is provided. This clinic happens once every month. During the first 3 months, 20 patients were considered (10 attendants, 9 virtually reviewed and 1 patient did not attend); 4 patients had a previous histological diagnosis (2 oligodendrogliaomas WHO grade II, 1 pilocytic astrocytoma WHO grade I and 1 ganglioglioma WHO grade I) and 16 patients were consider after initial presentation or follow-up of an incidental finding. As the main outcomes of this clinic: 12 patients were listed for surgery, 6 patients for follow-up (repeat imaging – 4 patients, neurology review – 1 patient, oncology review – 1 patient), and 1 was discharged. The EORTC QLQ - BN20 is completed prior to their consultation. We have found that 45% of patients feel ‘very uncertain about the future’ and 54% were ‘quite concerned about disruption to family life’. Overall, these statistics highlight the importance of this clinic in the global therapeutic approach of LGG patients.
Management and outcomes of incidental meningiomas: is routine follow-up required?

Oral

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BACKGROUND: 30% of newly-diagnosed meningiomas are incidental findings. There is no consensus on the optimal management of these patients. OBJECTIVE: To determine the clinical outcomes of patients diagnosed with incidental meningioma. METHODS: Single centre retrospective cohort study of patients diagnosed with an incidental meningioma between 2007 and 2015. RESULTS: 441 patients were included (459 meningiomas). Mean age at diagnosis was 63.3 years (range: 19-97); 348 female and 93 male. The main indication for MRI/CT was headache (25.9%). Median meningioma volume at diagnosis was 1.58 cm³ (range: 0.06-51.8). Commonest location was convexity (39.9%). At initial presentation, 6 patients underwent surgical resection, 50 were discharged and the remaining 385 entered surveillance imaging (1303 scans in total, 3.4 on average over a median of 36 months [range: 3-120]). Overall outcomes by the end of the study period were: 219 discharged, 12 lost to follow-up, 4 deaths (unrelated to their meningiomas) and 206 under continued observation. Of those 206, 38 (18.4%) (mean age: 52.9 years) had intervention (34 surgery, 2 stereotactic radiosurgery, 2 fractionated radiotherapy) after a median follow-up period of 24 months (range: 3-78). Indications for treatment were radiological progression (n=26), development of symptoms (n=6), and patient preference (n=6). Pathology revealed WHO grade I (benign) in 36 patients and WHO grade II (atypical) in 4 patients, of which one had recurrence 5 months after surgery and required salvage radiotherapy. For 231 patients discharged/lost to follow-up (mean age: 68.1 years), median follow-up duration was 18 months (range: 0-120). Nine patients (3.9%) had further MRI/CT for unrelated symptoms after a median of 37 months. CONCLUSION: The majority of incidental meningiomas do not require long-term follow-up and our data suggests that a 5-year period is sufficient. Further analyses of clinical and radiological predictors of growth and subsequent intervention are planned.
Medulloblastoma incidence and survival - a population based study

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Medulloblastoma can occur at any age, but is most frequent in infancy and childhood. There have been no previous detailed reports of incidence or survival across all age groups in the UK and few population-based reports internationally. This project provides for the first time population-based data on medulloblastoma incidence and survival across all ages in England.  

METHOD We extracted data for all patients with medulloblastoma diagnosed during 2001-2015, in England, from the English national cancer registry. The crude incidence rates per 100,000 were calculated, for all individuals and subdivided by age and 3/5yr periods. We also calculated 1-, 3-, 5- and 10-yr Kaplan Meier survival by 5-yr periods, for the overall cohort and by age group.  

RESULTS The overall average crude incidence rate was 0.12 per 100,000 (2001-2015), with no significant trend between 5-yr periods. However, the incidence rate for the age groups 0-3 and 4-14 was significantly higher than the older age groups. Male incidence was significantly higher than female. The 1-, 3-, and 5-yr (2001-2005) survival was significantly lower for infants than for older children. There was no significant difference in survival between children and the Teenage/Young Adult (TYA) group, for 5-yr and 10-yr survival. For all age groups, 10-yr survival was lower than 5-yr. All age 1-yr survival improved in the most recent period (2011-2015), 87.2% compared to 84.9% in 2006-2010. Individuals aged 4-14 and 15-24 had the highest 1-yr survival (2006-2010), 90.1% and 92.3% respectively, 5-yr (2006-2010), 64.0% and 76.9%, 10-yr (2001-2005), 65.4% and 63.6% respectively.  

CONCLUSION Medulloblastoma survival continues to decrease beyond 5-yr post diagnosis and varies by age group. Future investigation of whether variation in survival by age is related to systematic differences in tumour biology or in treatment could indicate ways of improving outcome for poorer-prognosis age groups.
Membrain project: provisional results of UK national, prospective audit on the management evaluation of metastases in the brain

**Oral**

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**OBJECTIVE:** To determine if brain metastasis referrals to the neuro-oncology multidisciplinary team (MDT) in the UK & Ireland comply with current NICE guidelines and to understand how patients are being stratified based on recursive partitioning analysis (RPA) and/or graded prognostic assessment (GPA).

**METHODS:** Prospective multi-centre national audit on all adult patients referred to the local MDT with ≥ 1 cerebral metastasis. After a 2 months trial at King’s College Hospital, neurosurgical units were invited to recruit patients prospectively for a period of 4 months from November 2017. Anonymised data on patient age, type/status of primary malignancy, performance status, location/number of metastases, available imaging, treatment recommendations and length to decision making was entered into a secure online database. Follow-up data will be collected after 12 months.

**RESULTS:** A total of 23/32 units participated. By end of February 2018 data on 579 patients (116% of initial target) had been submitted overall. Preliminary results from King’s College Hospital indicate a mean of 7 [range 3-13] referred cases per MDT. The median age of referred patients was 66 years [range 28-93 years] with 54.1% females and 45.9% males. Solitary metastases only comprised 44.6% of the referrals and specialist intervention (in the form of surgery or stereotactic radiosurgery) was only recommended in 48.0% of cases. The most common primary tumour was lung (33.8%) followed by melanoma (21.0%) and breast (21.0%); other comprised 24.4% (gastrointestinal 10.8%, renal 6.1%, cancer of unknown primary 4.1%, genito-urinary 3.4%). The national results will be presented at the SBNS meeting in autumn 2018.

**CONCLUSIONS:** The preliminary prospective data is in keeping with our previous audit results. This audit will help to draw up a national picture of brain metastases referrals and inform NICE on current work load and MDT management.
MicroRNA analysis of the invasive margin of Glioblastoma reveals druggable therapeutic targets in lipid metabolism pathways

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Heterogeneity of gene expression in Glioblastoma (GBM) has been recently recognised as a key feature involved in therapy resistance with invasive cells remaining after surgery and displaying unique molecular features. The dysregulation of small non-coding RNAs known as microRNAs (miRNAs) can disrupt gene regulatory networks and contribute to GBM development. However, the intra-tumour heterogeneity of miRNA expression in GBM has not yet been investigated. Here, we conducted microarray analysis using surgical specimens (n=72) sampled from the tumour necrotic core, proliferative rim and the invasive margin to show that different regions of the GBM tumour possess different miRNA expression profiles. We identified and validated two significantly upregulated miRNAs in the invasive margin compared to the core and the rim of the tumour. Functional studies using individual or combined overexpression of the two candidate miRNAs revealed that these miRNAs may act synergistically to target key enzymes involved in fatty acid oxidation (ACOX1 and CPT2) and lipoprotein uptake and secretion (LDLR). The expression of these gene targets was analysed in tumour samples by real-time quantitative polymerase chain reaction, flow cytometry and immunohistochemistry. These metabolic pathways will be further confirmed by liquid chromatography coupled with electrospray mass spectrometry (LC-ESI-MS). Our finding indicates that lipid metabolism may present a possible vulnerability of GBM invasive margin; indeed, pharmacological inhibition of CPT2 slowed the growth of patient-derived GBM cells. Understanding the function of miRNAs in regulating lipid homeostasis in GBM may provide novel avenues for GBM therapy.
miRNA expression and its functional effects in paediatric astrocytoma.

INTRODUCTION: Micro-Ribonucleic acids (miRNAs) are short non-protein coding RNAs involved in post-transcriptional regulation of genes by targeting the 3’ region of mRNAs. They have been associated with dysregulation of oncogenes and tumour suppressors (i.e. Myc and PTEN) and signalling pathways (i.e. PDGF and EGF) in many human cancers including adult high grade glioma (HGG). However, limited work has been published about their role in paediatric astrocytoma. Here, we examine the miRNA profile of paediatric astrocytomas of different grades, their correlation to survival and micro-vascularity and their function in proliferation, invasion and migration.

METHODS: The Nanostring nCounter miRNA array system analysed the expression levels of 665 miRNA sequences in 116 samples (101 astrocytoma tumours, 2 normal brain samples and 13 cell lines). Validation of selected miRNAs and their role in survival and micro-vascularity was studied by qPCR and immunohistochemistry. The functional effect of these miRNAs was evaluated by knock-down/knock-up of the sequences into the paediatric HGG cell lines SF-188 and KNS42 by transient transfection followed by Presto blue assay (assessing proliferation) and transwell assay in the presence (for invasion) or absence (for migration) of extra-cellular proteins.

RESULTS: 551 miRNAs were significantly expressed between HGG, low grade glioma (LGG) and normal brain. 89 of them exhibited fold-differences higher than 3, including miR-451, miR-149 and miR-21. The latter has known oncogenic effects in adult HGG and we also observed that its overexpression in SF-188 and KNS42 resulted in significant increased proliferation of more than double after 5 days. The comparison between HGG and LGG displayed differences in the expression of 10 miRNAs, with miR-34a down-regulated in HGG and correlating to loss of its chromosomal locus in 12-13% of tumours.

CONCLUSION: Specific miRNA profile signature of paediatric astrocytomas of different grades could potentially be used for prognosis and for identifying personalised therapeutic targets.
NEUROCOGNITIVE PROFILE OF PATIENTS WITH HEMISPHERIC LOW GRADE ASTROCYTOMA AND OLIGODENDROGLIOMA

INTRODUCTION Low-grade gliomas (LGG) can present with a wide spectrum of neuropsychological sequelae. This can significantly affect the quality of life of patients and their families and should be taken into consideration during all treatment decisions. METHODS This study retrospectively analysed, prospectively gathered pre-operative neurocognitive status for all patients undergoing awake surgery for subsequently confirmed LGG in eloquent areas. Data was analysed to explore whether exact histological diagnosis with molecular profiles (to distinguish astrocytoma from oligodendroglioma) had a direct bearing on the neuropsychological profile. Clinical and demographic data including gender, age, handedness, education, tumour location, seizure status and medication were recorded for all cases. Wide-ranging and comprehensive neurocognitive testing was performed. RESULTS Full results were achieved for 43 patients. Anticonvulsants were more common in the astrocytoma group than the oligodendroglioma group (p = 0.037). Where predicted Full Scale IQ was controlled for there were no significant differences between groups on Block Design (visuospatial ability); Similarities (verbal concept formation); Digit Span (working memory) or Verbal Fluency. There were significant differences in category fluency (p = 0.049), with the astrocytoma group attaining higher scores than the oligodendroglioma group. Where one-way ANCOVAs controlled for seizures the astrocytoma group demonstrated significantly higher scores in verbal (p = 0.04) and category fluency (p = 0.03); where anticonvulsant medication was controlled for differences between groups on these measures approached significance. DISCUSSION This represents the only known study examining the neurocognitive impact of astrocytomas vs. oligodendrogliomas. By utilising a comprehensive battery of clinically based neuropsychological tests taking into account baseline function rather than test means, we are able to identify potential impairments more easily and identify significant differences more accurately. Greater awareness of a “functional neurooncological” approach allows personalised treatment regimens targeted to maximise both survival and quality of life with both pre and post-operative counselling and neurocognitive rehabilitation.
Neuroimaging classification of progression patterns in glioblastoma: a systematic review

Oral

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BACKGROUND: Our objective was to report current neuroimaging classification systems of spatial patterns of progression in glioblastoma, report the terminology used to describe ‘progression’ and to assess the compliance of these studies with the Response Assessment in Neuro-Oncology (RANO) Criteria. METHODS: We conducted a systematic review to identify all neuroimaging studies of glioblastoma that have employed a categorical classification system of spatial progression patterns. Our review was registered with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) registry. RESULTS: From the included 157 results, we identified 129 studies that used labels of spatial progression patterns that were not (Group 1) and 50 studies that used labels that were based on radiation volumes. In Group 1, we found 113 individual labels and the most frequent were: local/localised (58%), distant/distal (51%), diffuse (20%), multifocal (15%) and subependymal/subventricular zone (15%). We identified 13 different labels used to refer to ‘progression’, of which the most frequent were ‘recurrence’ (99%) and ‘progression’ (92%). We identified 37% (n=33/90) of studies published following the release of the RANO classification were adherent compliant with the RANO criteria. CONCLUSIONS: Our review reports significant heterogeneity in the published systems used to classify glioblastoma spatial progression patterns. Standardisation of terminology and classification systems used in studying progression with neuroimaging would increase the efficiency of our research in our attempts to more successfully treat glioblastoma.
Cognitive impairment is detectable in the majority of patients presenting with primary brain tumour and is a major cause of disability, often being cited as the single greatest cause of burden to affected individuals and their carers (Locke et al. 2008). In addition, psychological reactions to diagnosis and treatment can include acute distress, anxiety and depression. Collectively, these symptoms may complicate treatment and influence quality of life (QoL). This presentation provides a rationale for the inclusion of neuropsychologists in neuro-oncology multidisciplinary teams. It summarises relevant outcomes of brain tumours and associated treatments and highlights evidence-based neuropsychological practice. This includes not only psychometric assessment but also cognitive rehabilitation and psychologically-based interventions (such as Problem Solving and Cognitive Behaviour Therapies). Learning outcomes include exposure to a specific assessment approach using the Neuropsychological Assessment Battery (NAB), components of cognitive rehabilitation, and the psychological impact of brain tumours.

Brain tumours kill more children and adults under 40 than any other cancer. Approximately half of primary brain tumours are high-grade malignancies known as glioblastoma multiforme (GBM). Current treatment regimes for GBM combine de-bulking surgery with radiotherapy and the chemotherapeutic DNA alkylating agent temozolomide (TMZ). However, the mean survival for GBM patients is ~15 months, with less than 10% of GBM patients surviving 5 years. This devastating prognosis highlights the urgent need for the development of novel agents to improve GBM treatment. A kinome-wide RNAi screen was carried out in a TMZ resistant GBM cell line. Cells were incubated with a low dose of TMZ and a non-toxic kinase-targeting RNAi. Cell viability was calculated by high-content microscopy and algorithm-based scoring of Hoechst-positive cells. Target validation studies of hits were carried out using additional RNAi libraries and small-molecule compound dose-escalation studies in additional GBM cell lines. We identify Extracellular Regulated Kinase 5 (ERK5) as a novel drug target to augment TMZ sensitivity. ERK5 is part of the MAPK signalling cascade, involved in cell survival and proliferation pathways, as well as cell differentiation and motility. ERK5 is dysregulated in many cancers and overexpression often results in a worse prognosis. At the mRNA level, ERK5 expression in GBM has been shown to be upregulated compared to normal tissue (REMBRANT Database). Using a range of siRNA and small molecule inhibitors in a panel of GBM cells, we have shown ERK5 inhibition sensitises GBM cell lines to TMZ. This will finding will be validated further using primary patient derived cultures and may potentially provide a novel target to improve GBM patient prognosis.
Image-guided biopsy of intrinsic brain tumours is a common neurosurgical procedure. In 2008 we reported the first UK series of day-case craniotomy and biopsy. In 2017 our unit presented a series of 645 biopsies over 10 years, of which 355 were discharged the same day. We now report the results of the first UK patient satisfaction questionnaire of day-case brain biopsy. Consecutive patients undergoing image-guided biopsies were sent questionnaires. All patients received sedation for their procedure and had a CT brain scan 6 hours postoperatively before discharge home.

RESULTS: Over nine months a total of 60 brain biopsies were carried out. 43 of these were identified as being suitable for day-case surgery and 39/43 were discharged 6 hours postoperatively. The remainder were thought to be unsuitable for day-case surgery. 32 questionnaires were sent out and 26 responses received. 24/26 patients felt involved in the decision making process to undergo a biopsy. Of the operation 8/26 remember nothing, 8/26 most of, and 10/26 remembered little of the procedure. 22/26 patients felt the timing of discharge was acceptable, only one thought they should remain in hospital for longer. All of the patients received adequate discharge information and felt supported once home.

DISCUSSION: Previous articles have demonstrated the safety of day-case image guided brain biopsies yet enhanced recovery programmes remain scarce in neurosurgery. Sustainability and transformation projects for the NHS require services to look at ways of reducing length of stay to reduce unnecessary admissions. Day-case neurosurgery is a practical option with clear significant cost saving implications. In the last 10-12 years our unit has challenged accepted practice and undertaken day-case and short stay neuro-oncology surgery. This satisfaction survey of day-case brain biopsies demonstrates that it is well tolerated and accepted by patients and imparts confidence to continue this practice.
Prognostic indices for brain metastases – which best reflects a UK cohort, and what is the prognosis of our metastasis patients?

Oral

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Many prognostic indices have been developed for patients with newly developed brain metastases; and have been analysed by different international groups, to find what the survival rates are for patients within different levels of each index. Our aim was to categorise our patients with brain metastasis into these indices, compare their survival to the previous analyses to find which best represented our cohort, and also to find which index best separates our patients into prognostic categories. The RTOG GPA, RPA, BSBM and diagnosis-specific GPA were assessed.

METHODS All patients who were referred, from January to June 2015, to Bristol Neuro-oncology MDT with probable diagnosis of solid intracerebral metastasis were included. Age, date of initial diagnosis, likely primary, KPS, number of intracranial metastases, status of systemic disease, management strategy and date of death. If the patients were still alive at time of data collection, their date of death was censored at 14/11/2017. Kaplan Meier survival curves were used for analysis, with Log rank tests to assess distinction between groups. A significance level of 5% was used.

RESULTS 83 patients were identified, with 11 alive at the time of data collection. Median age was 67 years. Median survival was 4.9 months, with 47% surviving 6 months or more, and 28% surviving over one year. 63.9% had extracranial metastasis, with 61.4% uncontrolled disease. The most common tumour was melanoma (24.1%), then lung (22.9%) and breast (14.5%). 6% underwent biopsy, 16.9% total excision, 36.1% palliative care, and 37.3% SRS. Our data most closely fit with the prognoses of Villa et al (2011) for the RTOG GPA, RPA and BSBM. However, there was no significant difference in the survival between different levels of prognostic index.

CONCLUSION More data is needed from multiple centres to establish the prognosis of patients with brain metastases in the UK.
Radiomic Features from Physiological MRI Shows Improved Accuracy over Structural MRI in Predicting MGMT Promoter Methylation in Glioblastoma

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O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation is widely used as an independent favorable prognostic factor in glioblastoma patients. However, the evaluation depends on the tissue obtained via surgery. The purpose of this study is to determine whether radiomic features of magnetic resonance imaging (MRI) can be used for predicting MGMT promoter methylation status, and to compare the accuracies of physiological and structural sequences in prediction. Pre-operative MRI scan was performed on 111 primary glioblastoma patients. MRI sequences include structural sequence (T1-weighted, T2-weighted, post-contrast T1-weighted and T2-weighted fluid attenuated inversion recovery [FLAIR]) and physiological sequence (dynamic susceptibility contrast-enhancement [DSC] and diffusion tensor imaging [DTI]). All images were co-registered to T2-weighted images. DTI and DSC were processed as previously. Mean diffusivity (MD), fractional anisotropy (FA), DTI-p and DTI-q were generated from DTI. The relative cerebral blood volume (rCBV), mean transit time (MTT) and relative cerebral blood flow (rCBF) maps were generated from the DSC. Radiomic features which describe the shape, margin, intensity histogram and texture of the tumor were extracted from each imaging modality. The least absolute shrinkage and selection operator (LASSO) regularization was used for feature selection. Support Vector Machines (SVM) was used for the prediction of MGMT promoter promoter methylation status, which was determined using pyrosequencing. A total of 15 features were selected from the structural imaging and 21 features were selected from the physiological imaging. An accuracy of 0.71 was achieved from the selected structural imaging features, while an accuracy of 0.79 was obtained from the selected physiological features. Our findings showed that radiomic features are useful in predicting MGMT promoter methylation status of glioblastoma using supervised machine learning schemes. Physiological imaging features may have the potential to make more accurate prediction than structural imaging features. Texture analysis may extract the most useful features for the prediction.
Rapid genetic classification of gliomas using Raman spectroscopy

Oral

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BACKGROUND: Raman spectroscopy probes the unique molecular vibrations of a sample to accurately characterise its molecular composition. No sample processing is required allowing for rapid analysis of fresh tissue. The genetic classification of gliomas, particularly isocitrate dehydrogenase (IDH) mutations, is critical for clinical decision-making. With the development of new drugs targeting specific glioma genetic subtypes it will become increasingly important for surgeons to be aware of the genetics of the tumour at the time of operation to inform their surgical strategy. The aim of this study was to use Raman spectroscopy on fresh samples taken straight from the operating theatre and to classify gliomas according to their genetic subtypes. Similar classification models were built using cryosections and formalin-fix paraffin embedded (FFPE) sections. METHODS: Raman spectra were collected using a Renishaw benchtop RA800 series spectrometer. Parallel sections underwent immunohistochemistry with targeted genetic sequencing when required to confirm the following five glioma subtypes: glioblastoma, IDH-mutated; glioblastoma, IDH-wildtype; astrocytoma, IDH-mutated; astrocytoma, IDH-wildtype; oligodendroglioma. RESULTS: Fresh tissue samples from 62 patients were collected (9 glioblastoma, IDH-mutated; 35 glioblastoma, IDH-wildtype; 10 astrocytoma, IDH-mutated; 2 astrocytoma, IDH-wildtype; 5 oligodendroglioma, 1 excluded). A principal component-linear discriminant analysis (PCA-LDA) model demonstrated 80%-95% sensitivity and specificity for predicting the five glioma genetic subtypes. For prediction of IDH mutation alone the model gave a 92% sensitivity and 91% specificity. 86 cryosection and 117 FFPE samples underwent Raman with models demonstrating 87-94% sensitivity and 77-80% specificity for predicting IDH mutations. In the fresh tissue samples, the mean time for spectra collection was 9.5 minutes with the whole process from tumour biopsy to genetic classification taking under 30 minutes. CONCLUSION: These results demonstrate proof of concept that Raman spectroscopy can be used for rapid, intraoperative glioma genetic classification. Further work is being done to refine model building to increase classification performance.
Reoperation in glioblastoma: is it worth it?

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The most common primary intracranial malignancy, glioblastoma (GBM) carries an exceptionally poor prognosis. Though first line management has seen some standardisation in recent years, the approach to recurrence is more heterogenous. To determine whether resection of recurrent GBM impacts survival, cases between January 1st 2015 and 31st December 2016 were retrospectively reviewed. Eligible patients had: (i) primary GBM; (ii) undergone resection for initial tumour (iii) received treatment for recurrence that could include chemoradiotherapy, reoperation or Gliadel. Data collected included tumour location and volume, extent of resection, ECOG, time to progression and death. Univariate and multivariate analyses were then performed. 136 eligible patients were identified with a median age of 61.5 years, of whom 78 (57%) were males. Tumours were predominantly temporal and frontal (70%), with a mean volume of 34300mm³. 36% of patients had initial gross total resection (GTR), with 81% going on to receive temozolomide and radiotherapy as part of the Stupp protocol. Median time to recurrence was 7.4 months, with 30 patients (22.1%) receiving reoperation; resulting in a significantly longer OS of 29.4 months compared to 13.5 in the non-reoperation group (P<0.05, 95% CI: 0.180-0.990, HR: 0.42), without an increase in morbidity when compared to first surgery. 15.4% of patients suffered complications at initial operation, while 12.1% did so at reoperation. (P>0.05). Cox regression analysis confirmed initial GTR as a significant predictor of survival, providing an OS of 20.5 months vs 16.4 months in the subtotal group (P<0.05, 95% CI: 0.220-0.870, HR: 0.44). MGMT methylation also significantly, positively influenced OS (P<0.01, 95% CI: 0.083-0.629, HR: 0.21), whilst an older age conferred a worse prognosis (P=0.02, 95% CI: 1.005-1.079, HR: 1.04). Overall, in keeping with existing literature, reoperation in recurrent GBM is shown to be an effective means of prolonging OS, without deleterious effects on neurological function.
Repurposing verteporfin as a potential new therapeutic to kill highly resistant, hypoxic glioma cells.

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Gliomas are highly malignant brain tumours derived from non-neuronal glial cells. These tumours are extremely aggressive with the most malignant form, glioblastoma, having a median survival time of less than one year, and unfortunately cannot be cured by existing therapies. These tumours are characterised by extensive areas of poor perfusion leading to severe hypoxia and subsequently high therapy resistance. Therefore, identifying cellular pathways and therapies that target the hypoxic microenvironment are likely to significantly improve patient outcome. One target could be the Yes-associated protein (YAP), which is a major effector of Hippo signalling involved in regulation of cell proliferation and tissue homeostasis. Recently, YAP has been suggested to play a role in glioma biology however, the nature of this role is unclear, as YAP activity is heavily dependent on cellular and microenvironmental context. Due to extensive hypoxic nature of gliomas, we investigated the effect of hypoxia on YAP activity and found through qPCR that YAP transcription and activity are increased under these conditions. Interestingly, treatment of both primary and immortalised adult glioblastoma cell lines with a YAP-inhibitor, verteporfin, resulted in almost complete cell death however surprisingly only under hypoxic conditions (1% O₂). Through in vitro assays and immunocytochemistry, we discovered that cell death was mainly through a non-traditional mechanism, with increased oxidative stress and vacuolisation of the cell, which was enhanced under hypoxic conditions. Verteporfin was also seen to avidly bind free iron, which potentially, through redox-cycling, increase oxidative stress. This porphyrin-like molecule is currently used in the clinic to treat wet macular degeneration and so our data suggests that verteporfin could be repurposed as a novel means to target this highly therapy resistant, hypoxic population of glioma cells.
Seizure prophylaxis in glioma - UK neurosurgical survey and clinical trial

Introduction

There is no consensus regarding the utility of prophylactic anti-Epileptic Drugs (AED) given to patients with supratentorial glioma before surgery, who have not had seizures. Newer AEDs have fewer adverse effects but their efficacy in preventing new onset seizures remains to be proven. In 2016, we surveyed all members of the Society of British Neurosurgeons (SBNS) to determine current practice and establish whether a randomised controlled trial (RCT) of AED vs no AED would be feasible.

Methods

Survey of neurosurgeons/centres dealing with glioma patients in the UK regarding:
(i) routine use of AED in patients with glioma
(ii) preferred AED
(iii) willingness to participate in a RCT of prophylactic AED
(iv) were patients seen in a dedicated specialist neurosurgical clinic before surgery.

A four point scale was used regarding usage of AEDs “almost always”, “usually”, “rarely”, “almost never” to avoid centering bias.

Results

71% of 35 respondents almost never prescribed AEDs while 14% almost always prescribed AEDs. 51.4% would use Levetiracetam, 11.4% phenytoin and 37.1% not applicable. 74.3% would be interested in participating in a RCT. 60% of patients were seen in a dedicated specialist neurosurgical clinic before surgery.

Conclusions

Based on responses of the survey a UK RCT trial of Levetiracetam vs no AED was considered feasible and a proposal (Seizure Prophylaxis IN Glioma - SPRING) was submitted to NIHR HTA. The application was successful. SPRING will start recruiting patients over three years from Jan 2019 in 15 neurosurgical centres across the UK.

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SERPINE1 identified as potential therapeutic target through RNA-Seq of clinically relevant invasive glioblastoma cells isolated from patients by 5-ALA based methodology

INTRODUCTION: We previously described a method to separate residual tumour cells from normal brain using fluorescent activated cell sorting (FACS). Using RNA-Seq on these cells we have identified new potential targets including SERPINE1, whose expression remains high in tumour cells as they invade into normal tissue. METHOD: 5-aminolevulinic acid (5-ALA) is a clinically used drug that facilitates fluorescence guided resection of glioblastoma (GBM). 11 tumour samples were dissociated and FACS used to separate residual fluorescent cancer cells (1%) from within normal brain. FACS sorted and unsorted mixed samples from tumour core, rim and invasive margin were compared. Gene expression was analysed by RNA-Seq and validated by qPCR, IHC and in vivo xenografts. RESULTS: Differential expression analysis identified 2567 genes with differences between core and invasive margin, and 78 genes with differences between 5-ALA FACS positive and FACS negative. Interestingly SERPINE1 expression is reduced in the unsorted invasive margin but expression remains high within sorted invasive tumour cells. Pathway analysis identified a predominance of immune system pathway changes between core and invasive margin. The differential expression of SERPINE1, VEGF, CHI3L1 and RTN1 in qPCR and IHC validated the same changes observed from the RNA-Seq data. The invasive and tumorigenic capacity of 5-ALA positive sorted tumour cells was confirmed by enhanced engraftment in a mouse flank model compared to unsorted cells, whereas non 5-ALA sorted cells failed to engraft. CONCLUSION: This study has demonstrated that 5-ALA fluorescent sorting of tumour cells from the invasive margin can identify new targets such as SERPINE1, whose high expression in invasive tumour cells would otherwise be overlooked. Our approach gives hope that we can interrogate the true residual disease, and for the first time gain insight into the source of tumour recurrence.
Shared decision making, the bridge between paternalism and autonomy.

Oral

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INTRODUCTION
Shared Decision Making (SDM) has been shown to be an effective tool in allowing patients to determine the treatment options best suited to their individual needs and is becoming the new standard of care in modern healthcare. It is invaluable in situations where reasonable options exist for a patient's management, such as Neuro-Oncology.

METHODS
A clinical decision grid was developed for three conditions, low and high grade gliomas and metastases. Three options were given to patients: best medical management or biopsy or resection (+/- adjuvant treatment) for gliomas and stereotactic radiosurgery or resection for metastases. The suitability, advantages and disadvantages were explained for each option and patients encouraged to choose the option that they felt suited them best. We analysed health care professional's attitude towards SDM before and after training using the Advanced Quality Alliance (AQuA) questionnaire. We assessed patient's response to consultations before and after the implementation of SDM using CollaboRATE questionnaire in the first cycle of a Plan Do Study Act (PDSA) process.

RESULTS
Five members of staff were trained in SDM and in response to the 19 point questionnaire (AQuA) there was an overall 28% improvement from 65% to 93% (in their attitude to SDM following training). The breakdown will be presented. 3 decision grids were used in 44 patients by 2 neurosurgeons and CollaboRATE scores remained high and did not change after full implementation with mean scores of 26/27 (range 15-27).

CONCLUSIONS
SDM is a useful process that allows patients to make informed decisions regarding their treatment options. Although a significant improvement was seen amongst staff following the introduction of SDM, no difference was seen in the patient response analysis. This may relate to the department already using this methodology prior to its full implementation and the lack of sensitivity of the CollaboRATE test.
Stereotactic radiosurgery for patients with melanoma and multiple brain metastases: experience during the era of immunotherapy and targeted agents.

Oral

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There has been significant progress in the treatment of metastatic melanoma, however the impact of new agents on patients with brain metastases remains poorly understood. We report outcomes using SRS for patients with melanoma brain metastases exposed to BRAF targeted agents and/or immunotherapy. METHODS Consecutive patients with metastatic melanoma and brain metastases undergoing SRS without routine whole brain radiotherapy were identified. Selection was restricted to patients having systemic therapy within the same centre. Follow-up included 3monthly MRI scans. All patients were treated using Cyberknife. The target volume was neuroradiology approved without an uncertainty margin. A review of electronic records and follow up imaging was undertaken. Survival data were summarized using Kaplan-Meier curves and compared via a logrank test. RESULTS 49 patients with 148 target metastases were identified. Median number of lesions was 2 (range 1-12), median dose 21Gy, median volume 0.31cc (range 0.01-6.71cc) and 94% had extracranial disease at 2 or more sites. Three patients did not have follow up MRI. One patient required long-term steroids, 1 had transient symptomatic swelling at 11months and 3 patients experienced bleeds (1 symptomatic- post-SRS treated lesion). 12-month local disease free survival was 71% (CI 53, 84). Distant brain progression occurred in 28 patients (57%), with a median time to progression of 8months (95% CI 5, 15). Distant brain progression was less frequent in patients with a single metastasis (p=0.03). Median overall survival (OS) was 11months (95% CI 8, 17). Median OS was 20months (95% CI 5, NR), 10months (95% CI 4, 12) and 11months (95% CI 3, NR) for patients with 1, 2-4 and ≥ 5 metastases respectively (p=0.07). CONCLUSION Beyond a single metastasis, the number of brain metastases did not correlate with OS. Patients with multiple brain metastases and active systemic disease may benefit from SRS however prospective evaluation is recommended.
Synergistic effect of targeted gene therapy with cisplatin for the treatment of medulloblastoma

Oral

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¹. Imperial College London

Medulloblastoma is the most common brain cancer in children, known for its high malignancy with a tendency to metastasize to the cerebrospinal fluid. Although, many patients have a high likelihood of long term survival with many free of disease after the conventional treatment, the survivors are at high risk of long term neurological side effects. Thus, development of new safer therapeutic strategies are urgently needed to improve the current treatments and the quality of life. To achieve a successful therapeutic strategy, we used Phagemid-AAV (PAAV) vector that is genetically engineered to express RGD4C peptide on the capsid to ensure binding to the tumour environment and subsequently enhance the selectivity through binding to integrins. This vector, carrying TNFα cytokine transgene, was used to treat human medulloblastoma cells in vitro as well as in vivo using tumour bearing mice. In the present study, we investigated the efficiency of our prototype (RGD4C-PAAV-TNFα) to selectively target medulloblastoma cells and deliver the transgene TNFα in vitro, using UW228 and Daoy medulloblastoma cell lines, as well as in vivo using tumour-bearing mice. The efficiency of the tumour cell death was further enhanced by low dose cisplatin. The data show that RGD4C/PAAV was selective in targeting TNFα gene therapy to the tumour. Further, RGD4C/PAAV-TNFα showed high efficiency in inducing tumour cell death, which was further enhanced by addition of cisplatin leading to necrotic as well as apoptotic cell death.
The accuracy of brain metastases contouring for stereotactic radiosurgery (SRS) by neuro-oncologists; what do the neuro-radiologist and neuro-surgeon add?

Oral

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Variability exists between clinical oncologists when contouring gross tumour volume (GTV) and normal tissue organs at risk (OAR) volumes. This variability is the ‘weakest link’ in the context of the highly conformal and highly accurate treatment delivery used for SRS. In 2016-17, NHS England commissioned 17 SRS centres. The service specification mandates “treatment protocols will ensure that target definition is performed by either a sub-specialised neuro-surgeon and/or neuro-oncologist (clinical oncologist) with input from a neuro-radiologist before a treatment plan is created.”. To evaluate the additional contribution by the neuro radiologist we analysed contouring conformality for all 47 patients treated in our centre between June 2017 and February 2018. GTV margins were contoured first by the clinical oncologist, and then copied and amended with input from the neuroradiologist and sometimes neurosurgeon. 1 mm margin was added to the GTV for the planning target volume (PTV). 47 patients, each with 1-4 metastases/resection cavities, resulted in treatment plans for 67 metastases/cavities. Doses used were: 15-24Gy in 1 fraction, 24Gy in 3 fractions or 25-30Gy in 5 fractions (if close to critical optic structures or brainstem). We used Eclipse TPS (v13.7) for Varian (Palo Alto, CA) Clinac iX with millennium MLC (5 mm) and Exactrac imaging system (Brainlab, Munich DE). All plans were created either using dynamic conformal arc (DCA) or VMAT RapidArc (RA) techniques with 6 MV photons and calculated using AAA (v10) on a 1 mm dose grid. Values for the final treated GTV and PTV (A) were compared with the GTV and PTV that were generated by the Clinical oncologist alone (B) will be compared using the Conformity analysis consisted of Jaccard coefficient, Dice coefficient, Geographical Miss and Discordance index as defined below. Results will be presented.
The development of an interdisciplinary assessment clinic to address the health related quality of life (HRQOL) issues of patients with a meningioma

Oral

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AIMS Evidence demonstrating the impact a meningioma brain tumour may have on the HRQOL of a patient undergoing neurosurgery has supported the development of an interdisciplinary assessment clinic and highlighted their therapeutic and supportive care needs. Meningiomas are often benign, yet they can have a complex presentation. NICE (2006) recommend that supportive care should be available for all brain tumour patients, however this can be limited for patients with a meningioma, as surgery is deemed to be curative and support has focussed on patients with malignant tumours. Self-reported HRQOL outcomes are now recognised as providing further understanding of the effects of the condition and treatments. The interdisciplinary clinic provides comprehensive Neuropsychology and Allied Health Professional assessment before and after surgery. The clinic, alongside addressing their needs, provides understanding of the physical and psychosocial effects of the tumour, to support rationalised clinical decision-making for proceeding with surgery.

METHODS The HRQOL of 30 consecutive patients attending the interdisciplinary clinic were compared before and six months following surgery using the FACT-BR, a disease-specific PROM and both were compared to normal controls. RESULTS The HRQOL of patients before and following surgery was significantly lower than normal controls. The HRQOL of 60% of patients improved and 40% deteriorated following surgery, although this was not statistically significant. The main issues before and following surgery were identified. CONCLUSION These results support that patients with a meningioma experience HRQOL issues, indicating the need for an interdisciplinary clinic to address their therapeutic and supportive care needs. The increase in incidental findings due to more frequent neuroimaging has also raised the importance of the need for careful consideration of the risk/benefits for proceeding with surgery, due to the potential negative impact on HRQOL, as conservative management may be preferable in some instances due to the slow-growing nature of the tumour.
The story behind the data: developing the conversation about brain cancer data beyond traditional indicators

Oral

Dr. Helen Bulbeck 1, Mr. John Broggio 2, Ms. Pesheya Doubleday 2, Mr. Will Jones 1, Dr. Jem Rashbass 2, Ms. Sally Vernon 2

1. brainstrust - the brain cancer people, 2. PHE

Background

brainstrust recognised a need to develop the conversation about cancer data beyond traditional indicators.

Methods

Since 2015, brainstrust has worked with the National Cancer Registration and Analysis Service (NCRAS) to:

• Explore data in new ways to address important questions for the brain tumour community.
• Establish a process that can be used by other cancer sites.

NCRAS produced Pilot Standard Output Tables for brain tumours covering incidence, diagnosis routes, treatment and survival. brainstrust explored the findings of this first data release and identified four themes on which to report, the first being Non Malignant Brain Tumours (NMBTs).

Results

1. NMBTs are a diverse group of tumours, including meningiomas, schwannomas, pituitary adenomas and other tumours.
2. About 9,000 primary brain tumours are diagnosed every year. 50% are non-malignant.
3. Over 1 in 10 people with a NMBT will not survive the first year (over 500 deaths annually).
4. When crude[1] and net[2] survival data is considered, there is no difference in the >49 age cohorts and the difference is smaller than 0.6% in the > 69 age cohorts.
5. 30% of people with a NMBT are diagnosed through A and E.

Conclusion

Key recommendations:

1. A need for public understanding, resources and information.
2. Support for people with a NMBT should be stratified more effectively according to a clear set of determinants.
3. Relevant and timely models of support should be developed, including high quality information and involvement of palliative support.
4. There must be parity of voice between non-malignant and malignant brain tumour community.

[1] Probability of death in the real world where you may die of other causes before the cancer kills you
[2] Probability of death in a hypothetical world where the cancer under study is the only possible cause of death
The survival of glioblastoma multiforme patients after burr hole biopsy based on their post biopsy treatment with or without chemotherapy and or radiotherapy.

Oral

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INTRODUCTION: Maximal safe resection of high-grade glioma is the recommended standard of care and the outcomes following surgery and chemoradiotherapy are well described in the current era. However, for some patients only a biopsy is feasible or is their preference. It is essential to understand the outcomes in this cohort in order to support shared decision making and informed consent. OBJECTIVES: To study the survival of patients with biopsy only confirmed glioblastoma (GBM). METHODS: Retrospective series over a three year period (2012-14). All patients who underwent burr-hole biopsy for GBM were included. Median survival was calculated from the time of biopsy until the time of death. Patients were stratified according to post-biopsy treatment. RESULTS: 84 patients were identified. Significant complications resulting in death or disability did not occur in any patients. The median survival of 33 patients who received best supportive care after biopsy was 1.66 months (mean 1.96 SEM 0.24); for those 15 patients receiving radiotherapy alone was 4.66 months (mean 7.68 SEM 2.11); 10 patients with chemotherapy alone was 4.26 months (mean 9.16 SEM 2.59); and for those 25 patients who received chemoradiotherapy was 9.73 months (mean 11.36 SEM 1.30). CONCLUSION: There is obviously a selection bias, with younger patients in best performance status and with favourable molecular profiles being offered more radical treatment. Nonetheless, this study provides valuable information for the consent process and shared decision making to help specialists and patients understand the outcomes following biopsy alone with different forms of adjuvant treatment and to compare these outcomes with other options such as resection.
Three-dimensional multicolour lineage tracing of intrinsic brain tumour models

*Oral*

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**INTRODUCTION:** Multicolour lineage tracing has provided striking demonstrations of stem cell tissue maintenance and development. Our objective is to gain insight into histogenesis, clonal expansion and migration of intrinsic brain tumours. We aim to investigate intratumoral heterogeneity through the identification of differently labelled clones but also the impact of different genetic lesions on tumour propagation. Combining multicolour tracing with advanced tissue clearing and image analysis we will interrogate these parameters in three-dimensions (3D).

**METHODS:** Rosa26-Confetti and Brainbow mice were crossed into lines containing different combinations of floxed tumour suppressor alleles. In this model, recombination is targeted to neural stem cells by intraventricular injection of a retrovirus expressing Cre recombinase and PDGFβ. Using this method multicolour tumours with histological hallmarks of human gliomas can be induced within 4 – 6 weeks. This rapid induction model will be used for the development of the methodology, including 3D image acquisition and image processing. Traditional sectioning and passive clarity (PACT) are used to prepare tissue for 2D and 3D imaging. This model of primary murine brain tumours will be complemented by a xenografting approach, using genetically characterised multiple human glioma initiating cell lines, genetically labelled with lineage tracing vectors. Tumour formation will be assessed with methods established using the retroviral model.

**RESULTS:** Retroviral injections induce tumour formation currently at an efficiency of ~50%. On frozen sections multiple colours are visible within all tumours representing the identification of different genetic clones. Tissue clearing has been successfully employed to image 3D volumes.

**OUTLOOK:** The presence of differentially labelled cells in our tumour model opens the potential for assessing clonal expansion and tumour heterogeneity.
Using qualitative research methods to optimise recruitment: The ROAM (radiation versus observation following surgical resection of atypical meningioma) Information Study

**Oral**

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**AIM:** ROAM is a randomised controlled trial comparing radiation to observation following complete surgical resection of atypical meningioma. We embedded a qualitative sub-study within ROAM with the aim of optimising patient recruitment. **METHODS:** Audio-recorded recruitment consultation (N=25), and semi-structured interviews with clinicians (N=14) and patients (N=22), including decliners and consenters. Analysis of transcribed audio-recordings was informed by content and thematic analysis. **RESULTS:** Analysis identified areas where communication was problematic. Giving patients their pathology results immediately before discussing ROAM left them overwhelmed and unable to absorb trial information. Interviewed clinicians were keen to participate in ROAM but some indicated concerns regarding the eligibility of patients at either ends of the age spectrum, believing such patients may not tolerate radiotherapy well. Clinicians’ presentation of the trial arms in consultations often lacked balance (emphasising the process and side effects of radiotherapy but providing limited information regarding active monitoring) and their terminology inadvertently led to misinterpretations among some patients. When interviewed, several patients struggled to see the logic of radiotherapy after hearing in previous consultations that further treatment was unnecessary. Patients who declined ROAM were concerned about the side effects of radiotherapy and viewed it as burdensome; many struggled to interpret key details of ROAM due to problematic communication. **CONCLUSIONS:** Embedded qualitative studies can identify barriers to recruitment in neuro-oncology trials and suggest ways to address these. We have amended the patient information leaflet, provided workshops and a webinar for oncologists and surgeons to enhance communication about ROAM, with the aim of optimising patient recruitment. Surgeons can aid recruitment by explaining to patients before surgery that they may be eligible for ROAM, if following surgery, they are diagnosed with atypical meningioma.
A case of metastatic gliosarcoma

Poster - C1

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Gliosarcoma is a rare malignant neoplasm of the central nervous system, consisting of both glial and mesenchymal components [1]. According to the 2007 WHO classification system, gliosarcomas are classified as a grade IV glioma and considered as a variant of the glioblastoma [2]. Gliosarcomas represent approximately 2 - 8% of all glioblastomas and approximately 0.48% of all intracranial neoplasms [2]. Small scale reports of non-metastatic gliosarcoma suggest that they are typically IDH1 wildtype, with high rates of TERT mutations and about a third carrying a MGMT promoter methylation [5]. Compared with glioblastoma, gliosarcomas have a lower rate of EGFR amplification [1,2] and a high rate of TP53 mutations (31% in glioblastoma vs. 70% in gliosarcomas) [1,6]. There is also evidence that a high prevalence of TP53 mutations is associated with poor survival and an epithelial-mesenchymal transition signature in gliosarcoma patients [6]. Fewer than 20 cases of metastatic gliosarcoma have been published to date [7-10]. Previous case reports have focused on the extent and location of metastases, rather than their molecular profile. We report the case of a 59 year old male patient with a primary gliosarcoma of the right temporal lobe. He proceeded to a stealth guided craniotomy and resection. Immunohistochemistry showed GFAP focally positive but predominantly negative, Ki67 50%, IDH 1 mutation R132H negative, reticulin prominent pericellular staining in GFAP-negative areas, ATRX strongly positive, S100 focally positive and synaptophysin negative. He then progressed rapidly despite radical chemoradiation with 60 Gy in 30 fractions and adjuvant Temozolamide. He died from intracranial and extracranial metastases to the skull, soft tissue, lungs, pleura and liver within three months of presentation. Cannonball lung metastases are shown in the imaging. The relevance of molecular profiling in such cases is discussed.
A dedicated neuro-oncology clinic for teenagers and young adults

Poster - D5

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INTRODUCTION: Central Nervous System tumours are amongst the most common group of neoplasms in Teenagers and Young Adults. It is widely recognised that these young people have specific physical and emotional needs. Transition for survivors of children with CNS tumours is also a key issue; particularly as these tumours carry a high incidence of late effects and may frequently have ongoing neurosurgical issues that require monitoring or treatment. With this in mind, a Liverpool-based TYA neuro-oncology service was established that centres on a dedicated neurosurgical clinic, joint adult/paediatric operating and MDT discussion crossing both age groups. METHODS: The TYA clinic was established in June 2013 and is jointly led by ‘adult’ and ‘paediatric’ neuro-oncological surgeons with additional multidisciplinary input including CNS Nurse specialists and psychologists. Referred patients include paediatric patients reaching 18 years of age who continue to require tumour surveillance in an adult setting (particularly those with residual low-grade neoplasms) and new patients in the 18-25 age group requiring input by surgeons from both sectors. RESULTS: 93 individual patients (median age 20.2 years) have been seen in 231 clinic episodes with an average of 6.7 patients per clinic since January 2016. Most patients were treated for childhood tumours: 38 low grade glioma, 8 tectal plate tumour, 6 medulloblastoma etc. Most had surgically treated tumours, although 26 patients had had radiation and 20, chemotherapy. 11 patients had pineal cysts referred directly to the clinic and generally followed for 1-2 years and then discharged. Patient feedback was highly favourable. DISCUSSION: The TYA Brain tumour clinic has been shown to complement our transition and tumour late effects service well. Patients appreciated it as a useful and dedicated resource for the TYA population prior to transition to a full adult neurosurgical clinic. Our experience supports the development of dedicated TYA neuro-oncological services.
A nurse led clinic improves care for patients with Glioblastoma and tumour treating fields.

Poster - D13

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INTRODUCTION Poor prognosis and limited access to clinical trials can result in a poor hospital experience for patients diagnosed with Glioblastoma. The role of the clinical nurse specialist (CNS) is pivotal to improving patient experience. TTF (Tumour treating fields) is a novel, non-invasive technique using electrical fields to disrupt cell division, and requires monthly review. Utilisation of a nurse led clinic co-ordinating the TTF patient pathway was examined.

METHOD All patients in the North West of England on TTF required monthly compliance data collection and assessment by an Optune team member, and three monthly clinical and radiological review as well as ongoing oncological review. A nurse led clinic for patients meeting the criteria for the study was developed, providing co-ordination, holistic needs assessment, support, advice and signposting for patients and carers. Data collection includes EORTC quality of life measures, patient and carer satisfaction surveys and device compliance data.

RESULTS 4 patients have been having treatment for up to 8 months. Clinical visits occur monthly, with imaging and clinical review when required, occurring at the same time as Optune team member review. Device compliance is >80%. There has been a 0% DNA rate, and patients report a positive experience in the clinic setting. The clinic has allowed a buddy system to be developed for patients and carers.

CONCLUSION Novo TTF remains prohibitively expensive and is a labour intensive device for both patient and healthcare professional. Using a nurse led clinic for clinical review and to coordinate appointments and investigations has reduced patient outpatient attendance, and improved patient experience. Further reduction in cost may be possible by compliance data being collected by the specialist nurse obviating the need for direct on site company support.
An audit of the management of elderly patients with glioblastoma in the UK: have recent trial results changed treatment?

INTRODUCTION. A new treatment option for elderly patients with glioblastoma (GBM) became available in June 2016 with Perry's presentation at ASCO showing that hypofractionated radiotherapy (40Gy in 15#) with concomitant and adjuvant temozolomide improved survival compared to hypofractionated radiotherapy only. We investigated uptake of this treatment regimen in two UK oncology centres. METHODS. This retrospective study involved patients from NHS Greater Glasgow and Clyde and Brighton and Sussex University Hospitals. Patients aged 65 or over with a histological or radiological diagnosis of GBM were identified from multidisciplinary meeting and clinic lists between July 2016 and December 2017. RESULTS. 141 patients were identified. 72 had a pathological diagnosis and 69 had a radiological diagnosis of GBM. 23.6% of patients with a pathological diagnosis exhibited MGMT promoter methylation. Median age was 74.4 years and 43.3% of patients were female. 57.7% received at least one oncology appointment. 18.4% of patients received chemotherapy and radiotherapy, 8.5% chemotherapy only and 6.4% radiotherapy only. 63.8% did not receive either chemotherapy or radiotherapy. 63.8% did not receive either chemotherapy or radiotherapy. Patients who received treatment had a significantly lower median age at diagnosis than patients who did not receive treatment (69.4 years v. 76.8 years, P=0.000). Median overall survival was 6 months. Of 26 patients receiving radiotherapy and concomitant chemotherapy, 46.2% received hypofractionated radiotherapy and the remainder received standard radiotherapy (60 Gy in 30#). Median survival for both groups was 12 months (P=0.991). DISCUSSION: While both centres adopted the hypofractionated chemoradiation schedule, a significant proportion of elderly GBM patients received standard chemo-radiotherapy. Importantly, median survival of patients receiving hypofractionated chemo-radiotherapy was equivalent to that of patients receiving long course treatment. The shorter treatment time, better side effect profile and equivalent survival outcomes of the hypofractionated regime indicate that it should be used more widely in the management of GBM patients aged over 65.
Analysis of cranial adult pilocytic astrocytomas over a 10 year period.

**Poster - C7**

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OBJECTIVES: Review of clinical features and outcomes in patients with adult pilocytic astrocytoma (PA). DESIGN: Retrospective study of all adult PAs treated in our centre using clinical & pathological data. SUBJECTS: 55 cases of pilocytic astrocytomas (>16 y old). METHODS: All adult patients with histologically proved cranial PA operated between 2007 and 2017. Analysis was performed using STATA 11.0 (StataCorp LP). RESULTS: 55 patients with PA were reviewed: 26 M/29 F. 9 had NF 1. PA was first diagnosed in childhood in 12 patients. Patients diagnosed before 18 years experienced a greater number of recurrences (p=0.023). Mean follow up was 8.4 years. The most frequent tumour locations were the cerebral lobes (41.8%) and cerebellum (32.7%). PA WHO grade I was confirmed histologically in 89.9% of cases. 22 patients underwent radiotherapy, of which 8 (36, 6%) had also chemotherapy. Tumour recurrence occurred in 19 patients (34.5%). WHO grade was an independent predictor of tumour recurrence (p=0.02). Of the 19 recurrences, 5 (26.4%) had a total/near total resection (p=0.014). Patients with incomplete resections had higher rates of post-surgical radiotherapy (p=0.018). Progression-free survival was longer in patients with WHO grade I tumours that had total resection. Radiotherapy did not improve progression-free survival rates (p=0.54). CONCLUSIONS: Recurrence in PAs seems to depend on the age of first diagnosis. WHO grade and extension of resection were independent predictors of progression-free survival, although resection was largely dependent on tumour location. Adjuvant radiotherapy in incomplete resections did not impede disease progression although mean times to recurrence were longer in the radiotherapy group.
Autophagy induced cell death of paediatric brain tumours by glucose restriction.

Poster - A9

Mr. George Lockwood ¹, Ms. Janhavi Apte ², Dr. Delyan Ivanov ³, Ms. Rebecca Parr ⁴, Prof. David Walker ¹, Dr. Lisa Storer ¹, Prof. Richard Grundy ¹


Brain tumours are the leading cause of cancer related death in children and are the most challenging childhood cancers in relation to diagnosis, treatment and outcome, both in terms of mortality and morbidity. One potential strategy to improve outcomes is to exploit the metabolic differences between normal and tumour cells. Under normal physiological conditions, brain cells metabolise glucose for energy. Under glucose deprivation they instead metabolise ketone bodies (KBs). Mitochondrial defects in brain tumours reduce this metabolic flexibility resulting in dependence on glucose. Therefore, a high fat, low carbohydrate ketogenic diet (KD) may control tumour growth. We evaluated glucose restriction on Ependymoma (BXD-1425, Epn1) and pHGG (SF188, KNS42) cells using glucose concentrations; 17mM, 10mM (diabetic), 5mM (physiological), 3mM (hypoglycaemic), 1mM and 0mM +/- KBs. After 5 days, spheroid volume and metabolic activity were assessed and immunohistochemistry was performed for Ki67 (proliferation), caspase 3 (apoptotic cell death), p62 and LC3B (autophagy), OXCT1 and BDH1 (ketolytic enzymes) and PKM2 (glycolytic enzyme). There were no significant differences in metabolic activity as glucose concentration decreased, however, spheroid size decreased and could not be rescued by KBs. All cells had low expression of OXCT1 and BDH1 and were positive for PKM2 with no significant variation in protein expression at different glucose concentrations. This implies that these cells are likely to respond well to the KD. Ki67 was moderately expressed at all glucose concentrations. Caspase-3 remained low regardless of glucose concentration. Both LC3b and p62 showed increasing expression as glucose concentration decreased (unaffected by KBs). This, alongside the decrease in spheroid size indicates that these cells were unable to adapt to decreasing glucose concentrations and initiated autophagy but not apoptosis. This indicates that Ependymoma and pHGG tumour cells are dependent on glucose for growth and provides further evidence that these patients may respond to the KD.
CaFLe: A novel naming test for use during awake craniotomy for tumour resection.

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Confrontation naming tests are widely used techniques for assessing language function in people with dominant hemisphere pathology. Tests that vary in difficulty allow the assessment to be matched to the educational and intellectual level of the patient. For example, somebody with an extensive premorbid vocabulary and mild injury to the language areas of the brain will easily retrieve common words – their word finding impairment only becomes apparent with less common items. Conversely, somebody with limited educational attainment may need to be assessed using a range of common items to avoid falsely identifying pathology rather than premorbid limitations. This study aimed to assess the validity and utility of a novel naming test, the CaFLe, for use during awake craniotomy for tumour resection. Our surgical protocol involved pre-assessing patients with the CaFLe alongside other neuropsychological tests. Items that could be named at baseline were incorporated into the intraoperative assessment. Better performance on the CaFLe at baseline was found to be associated with better performance on the Graded Naming Test ($r(29) = .61$, $p < .001$, $r^2 = .37$), showing the novel CaFLe has convergent validity with an established graded difficulty naming test. The CaFLe was deployed during direct electrical stimulation and repeatedly throughout the course of resection. Surgeons were immediately notified of word finding difficulty if and when it became apparent. As shown in our poster, use of the CaFLe pre- and intraoperatively demonstrates that it is sensitive to relatively subtle language deficit and can be predictive of focal seizures.
Can a local neuro-oncology database contribute to clinical research? A feasibility study

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Background – More detailed research is needed on the incidence and survival of patients with gliomas, particularly in relation to possible associations between age, sex, ethnicity, tumour morphology and biomarkers. This feasibility study aims to evaluate the neuro-oncology database at King's College Hospital NHS Trust for data quality and completeness in order to compare the incidence and survival with previously reported results.

Methods - A review has been conducted on data for all adult patients with gliomas diagnosed between 1st January 2015 and 31st December 2016 and discussed in the Multidisciplinary Team (MDT) at King's College Hospital NHS Trust. These data were extracted from the local neuro-oncology database and included information on demographic characteristics, tumour type, referral and treatment. Data were then cross-checked against the patients’ MDT reports and neuropathology records for accuracy and validity.

Results – Data on 280 patients diagnosed with glioma during the study period were included in the database. After checks for completeness and validity, most data items had good completeness and were generally of good level of accuracy. For example, age, sex, tumour morphology and tumour location were 100% complete, biomarkers were 91-99% complete and assigned ethnicity was 75% complete.

Conclusions – After quality assurance, the data quality and completeness for 280 gliomas recorded in the neuro-oncology database at King's College Hospital NHS Trust during the years 2015 and 2016 was generally high. This suggests there is potential to use these data over an extended study period to answer clinical research questions.

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INTRODUCTION: There is an urgent need to expedite the development of new or repurposed drugs for children's cancer. An additional challenge in the developing brain is to ensure the drug is delivered to the tumour at therapeutic and non-toxic concentrations for sufficient duration to achieve the biological effect. Children's brain tumours account for over 20% of childhood cancers and differ significantly in their biological characteristics from their adult counterparts. METHODS: The authors participated in an international CNS drug delivery workshop funded by the charity Children with Cancer UK in February 2016, where different experimental techniques aimed at optimising CNS drug delivery in children's brain tumours were discussed. RESULTS: The workshop was reported by e-cancer (http://ecancer.org/journal/10/full/630-highlights-of-children-with-cancer-uk-s-workshop-on-drug-delivery-in-paediatric-brain-tumours.php; http://ecancer.org/conference/831-drug-delivery-in-paediatric-brain-tumours.php). We were encouraged to develop a proposal to establish an international research consortium to raise awareness and promote collaboration in the field. This is now funded for two years by Children with Cancer UK. The Children's Brain Tumour Drug Delivery Consortium seeks to strengthen collaborative developments by working closely with the international children's brain tumour community, encouraging and facilitating discussions between a multi-disciplinary network of clinicians and researchers within pharma and academia as well as a range of funders and stakeholders. As of March 2018, we have 94 individuals from 11 nations registered as members, with diverse stakeholders represented by academics, clinical academics, charities, public/patient groups, industry and regulatory bodies. CONCLUSION: We present this abstract to the BNOS conference to raise awareness of this initiative with the large number of relevant stakeholders who will be attending the event, and to extend our invitation for collaborators to join the consortium.
Circulating miR-9 levels as a novel prognostic biomarker for higher-grade meningioma

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Introduction: Meningioma is the most common primary tumour affecting the central nervous system; it is classified as benign (WHO I, ~80%), atypical (WHO II, ~15-20%) and anaplastic/malignant (WHO III, ~1-3%). The 3-year recurrence rate in WHO I meningioma is estimated in about 50% and it is much greater in WHO II and III tumours. MicroRNAs (miRNAs) represent a large class of small RNAs driving regulation of gene expression at post-transcriptional level and playing a role in cell proliferation, differentiation, apoptosis and carcinogenesis. Several studies showed that miRNAs are involved in tumour progression and therefore proposed as diagnostic tools. In this study, we evaluated miRNA signatures in meningioma to identify novel biomarkers of tumour progression.

Methods: Meningioma specimens were collected from consented patients, according to the ethics. The 96-miRNA profiling was established using the Quantimir Cancer MicroRNA qPCR Array (System Biosciences, UK) following the instructions of the supplier and validation studies performed using TaqMan® MicroRNA reagents (Applied Biosystems). Bioinformatics analysis was conducted using the NormFinder software and Morpheus (Broad Institute, Cambridge, MA). Probability (p) values were calculated using the Student’s t-Test, p<0.01 or 0.05 ± SEM.

Results: We established a new miRNA dataset by identifying eight miRNA signatures (p<0.01) differentially regulated in benign versus malignant meningioma cells (miR-9, -10b, -125b, -126, -134, -143, -145 and -199). Validation studies confirmed that the miR-9 is upregulated in malignant KT21-MG1 cells (10.71 folds-Log2 scale, p=0.0006) and WHO III tissues (3.75 folds-Log2 scale, p=0.044). In addition, analysis of mRNA cargo of WHO II-III (n=11) derived serum exosomes showed an increased miR-9 levels (1.76 folds) when compared to WHO I (n=9) samples.

Conclusion: Our novel data suggest that the miR-9 is upregulated in a cohort of mRNA cargo-blood exosomes derived higher-grade meningioma patients, supporting further investigations as possible circulating biomarker of tumour progression.
Circulating miRNA expression in glioblastoma patients & its effect on cell migration

Poster - A5

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Glioblastoma Multiforme (GB) is the most common malignant human glioma and is currently incurable. Further understanding of the epigenetic mechanisms underpinning GB progression could facilitate earlier diagnosis and improve prognosis.

MicroRNAs (miRNAs) are regions of RNA that reduce translation of proteins. Identifying dysregulated circulating miRNA(s) in sera could provide a potential biomarker for diagnosis, accessible through a blood test.

GB and control sera supplied by BrainTumour North West tissue bank was used to profile the circulating expression of miRNAs -20a, -34a, and -92a using quantitative PCR technology. The results were analysed according to age and sex, as well as overall comparison.

MiRNA20a was reduced in GB samples as well as in 20-39 year-old (yo), 40-59 yo and male GB patients, but increased expression in GB patients aged 60 and over. MiRNA92a expression was reduced in 40-60 yo GB patients however GB patients over the age of 60 showed an increased expression. MiRNA34a was reduced in GB patients overall, in both sexes and two out of three age groups (40-59, and 20-39 yo) when compared to age and sexmatched control samples.

The effect of miRNA 34a on cell migration was analysed in human glioma and control human astrocyte cell lines by overexpression and knockdown. The cell lines were cultured in media containing pooled sera from GB patients, healthy individuals, standard fetal bovine serum and exosome depleted serum. Wound healing assays were performed to ascertain cell migration. Inhibition of miRNA 34a-5p significantly increased rate of migration in glioma cells cultured in human control sera.

Acknowledgements should be made to Brain Tumour North West for providing the serum samples used in this study.
Comparing neurosurgical intervention survival outcomes for intracranial metastases in patients with known or unknown primary tumours

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INTRODUCTION Patients with intracranial metastases from an unknown primary tumour (CUP) are often not put forward for the same treatment and benefits as those provided for patients with metastases of known primary tumour origin (CKP). NICE recognised, in their 2010 guidance, the current lack of national research strategy to address the needs of CUP patients with brain metastases. NICE has previously recommended increasing the collection of epidemiological data regarding these patients. AIM To compare survival of CKP patients undergoing resection of intracranial metastases with survival of CUP patients also undergoing resection. METHODS A retrospective study was performed to compare survival between the two patient groups (CKP and CUP). Patients were sampled from a pathology database (age range 20 – 83; median age 61). Data was then collected from patient notes and trust information services using a proforma. INCLUSION CRITERIA Surgically managed patients, aged over 18 years old, with a histological diagnosis of intracranial metastasis during the study period 01/01/2008 – 11/04/2018. RESULTS 324 patients identified of whom 28 were censored (8.6%). This included 265 (81.8%) CKP patients of whom censored 24 (9.1%). 59 (18.2%) CUP patients of whom censored 4 (6.8%). Median survival for CKP patients was 10 months (95% CI 8.509 – 11.491); for CUP patients it was 6 months (95% CI 4.263 – 7.737). Log rank (Mantel-Cox) p = 0.747. CONCLUSION The data reveal no statistically significant difference in survival outcome between the two groups. This is in keeping with the findings of the limited number of other studies in this area, and suggests that current diagnostic pathways specifying a thorough search for identification of primary tumours before surgery may not improve patient outcomes. Surgical management of CUP brain metastasis patients is therefore an appropriate treatment option in this patient group.
Correlation between APT-CEST and 18F-Choline PET in glioma at 3T

INTRODUCTION: Chemical exchange saturation transfer (CEST) MRI is emerging as a powerful diagnostic tool in gliomas but there is lack of agreement as to the source of the Amide Proton Transfer (APT)-CEST signal and contrast. We aimed to investigate whether APT signal could be a non-invasive biomarker of Teenage and Young Adult (TYA) glioma cell proliferation through correlation with $^{18}$F-Cho PET SUV as the gold standard. 

METHODS: 8 TYA patients referred for $^{18}$F-Cho PET-MRI with suspected glioma were recruited for APT-CEST acquired with a gradient echo based snapCEST acquisition (12 studies). Regions of interest (ROI) of the ‘non-enhancing’, ‘enhancing’ and ‘necrotic core’ in the tumour and healthy ‘white matter’ (WM), were segmented from T2w-FLAIR and T1w-postGd images. 

RESULTS: The strongest correlation was observed for APT-CEST versus $^{18}$F-Cho PET ($\rho = 0.85$, $p<0.001$) and the highest APT-CEST signal was seen in the enhancing and necrotic core ROIs. APT-CEST distinguished the non-enhancing tumour ROI from normal white matter ($p<0.001$) whilst $^{18}$F-Cho PET SUV could not ($p>0.05$). 

DISCUSSION: This feasibility study presents the first comparison of APT-CEST and $^{18}$F-Cho PET in patients with TYA gliomas. The strong positive correlation indirectly demonstrates that APT-CEST may be a marker of glioma cell proliferation and further demonstrates the potential of APT-CEST in the assessment of glioma burden. Importantly, APT-CEST could be a useful adjunct in monitoring disease activity in $^{18}$F-Cho negative non-enhancing tumour.
Cross-centre reproducibility of advanced quantitative diffusion parameters for neuroncology assessment

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Purpose: Quantitative DWI provides putative imaging biomarkers for glioma characterisation and early response assessment; cross platform validation is essential for implementation in clinical practice and multi-centre trial platforms. This work compares reproducibility of advanced diffusion parameters, derived from mono-exponential, IVIM and stretched-exponential models in phantoms and the brains of healthy volunteers (HV) across multiple scanners.

Methods: Ice water and Biomimetic phantoms were imaged on three different MRI systems and HV on two systems. The protocol included low b-value acquisitions from which ADC and IVIM parameters; D*, D and f were calculated and high b-value acquisitions from which the stretched parameters, DDC and α were derived. Coefficient of variation (CV) was calculated for each DWI parameter.

Results: In ice water phantoms, ADC values were highly reproducible, as were DDC values; with CV 1.40-4.01% and CV 0.51-4.22% respectively. ADC was again reproducible across all biomimetic phantoms with CV’s <5.64%. The highest DDC CV was 7.84% in one phantom, but the remainder were <5%. CV of DDC in grey and white matter in vivo ranged from 13.41-16.79%. Discussion: DDC measures in phantoms show good reproducibility similar to ADC, in accord with previous studies of ADC variability across centres. Slightly higher CV in vivo, where biological heterogeneity in tissue will also contribute to variability, also accords with published ADC data. Poorer reproducibility of DDC compared with monoexponential and IVIM parameters may reflect influence of more complex diffusion components sampled over a wider range of b-values and lower signal to noise ratio in a ‘high b-value protocol’. Conclusion: Ice water and biomimetic phantoms provide useful assessment of cross-platform variability, however further study of spatially-heterogeneous systems with multiple intravoxel diffusion components are important for realistic evaluation of in vivo reproducibility of parameters from complex diffusion models.
Development of nanoparticles with ‘improved drug loading’ for local delivery to the brain in the treatment of medulloblastoma

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Poor CNS penetration by cancer drugs limits their application in sensitive brain tumours such as medulloblastoma. An alternative approach, delivering drugs directly to residual tumour using nanoparticulate delivery systems (NPDS) could reduce some of these problems. The main challenges hindering the clinical translation of the use of NPDS for local delivery of drug to the residual tumour are inadequate drug loading and erratic release. This study focuses on understanding the conditions required for the development of a NPDS with sufficient drug loading for post-surgical delivery to the residual tumour. This was done by selecting known effective drugs; Etoposide, etoposide phosphate and teniposide and matching them with modified poly (glycerol) adipate based polymers based on the interactions observed between them. Fourier transform infra-red spectroscopy (FTIR), contact angle measurements and drug release experiments have been used to screen the drugs and substituted PGAbased polymers. Based on the interactions observed, polymers were matched with the specific drugs. Two types of drug nanoparticles were prepared from these combinations. Drug loaded matrix polymer nanoparticles (NP) were prepared by an interfacial deposition method and a novel process of applying a polymer coating to drug nanoparticles, polymer coated drug nanoparticles (PCDNP) was also developed. The following drug loading results were obtained for etoposide (NP: 5%, PCDNP: 77%) and teniposide (NP: 23%, PCDNP: 32%). This systematic approach to monitor drug and polymer interactions to match polymers to drugs resulted in the formulation of nanoparticles with higher drug loading.

Keywords: Medulloblastoma, Nanoparticles, Etoposide, Etoposide phosphate, Teniposide, Poly(glycerol)-adipate
Developments in molecular pathology testing for glioma

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Genetic analysis is now an integral part of glioma diagnosis and an essential aid to stratification of patient care (Louis et al., 2016). University Hospital Southampton is expanding its test repertoire to reflect these needs. The sensitive and specific technology of droplet digital PCR (ddPCR) can move Isocitrate Dehydrogenase (IDH) mutation testing away from current subjective immunohistochemistry (IHC) methodology. In a small study, 26 cases were tested by IHC, ddPCR and Sanger sequencing. Twenty cases were concordant for IDH R132H by IHC and ddPCR analysis, whilst three cases harboured the rarer IDH R132 or IDH2 variants, not evaluated by these two tests. However, three remaining IHC-IDH1 R132H negative cases were positive for IDH1 R132H by ddPCR, illustrating an improved sensitivity for IDH mutation testing using the digital PCR platform.

Generic testing workflow for ddPCR, that meets ISO 15189 accreditation standards, facilitates a quick test work up for Single Nucleotide variant (SNV) mutation analysis. This can support clinical decision making vis-à-vis targeted therapy options and potential clinical trials entry. The use of microsatellite markers analysis provides an alternative method for the evaluation of 1p19q deletion characteristics. Investigation of O⁶-methylguanine-DNA methyltransferase (MGMT) promoter methylation status using high resolution melt (HRM) brings this test in to our standard molecular laboratory workflow. Molecular testing for MGMT methylation status delivers results with fast turnaround time, supporting timely, evidence-based decisions for Temozolomide treatment. The PCR-based nature of these analyses have minimal tissue requirements and this suite of tests can be run on a single sample.

Participation in the 100,000 genomes project is providing whole genome data with which to explore a ‘one stop shop’ approach to glioma molecular testing. In combination with DNA methylome analysis, we wish to evaluate the clinical utility of a pan-genome analysis for our glioma diagnostic and prognostic support service.
Diagnostic Interval for paediatric patients presenting after the HeadSmart campaign: experience in a district general hospital.

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INTRODUCTION: The HeadSmart Campaign was launched in June 2011 and aimed to improve awareness and recognition of brain tumours in children. The aim was to reduce the diagnostic interval in the UK from an average of 14 weeks to 5 weeks, which was the best-reported international level. Here we set out to assess the diagnostic interval for patients presenting to our district general hospital.

METHODS: All paediatric patients (0-18 years of age) who were diagnosed with a brain tumour at our unit between 1st July 2011 and 31st December 2017 were identified using the International Classification of Diseases (ICD-10) coding. A retrospective review of all patients’ notes was performed to collect data on patient demographics, presenting symptoms, previous presentations and patient outcomes.

RESULTS: 6 patients were identified, ranging from 6 weeks to 10 years of age (median age of 6.5 years). There were 5 females and 1 male. The median diagnostic interval in our cohort was 2.5 weeks (range 1 day-2 months) with 4 cases (66.7%) below the 5-week target. The median number of documented presentations prior to diagnosis was 4 (range 0-7). There was a range of subsequent diagnoses including: a medulloblastoma type 4, a choroid plexus papilloma, two pilocytic astrocytomas (one grade I and one grade II), an anaplastic ependymoma and a diffuse intrinsic pontine glioma. The most common presenting symptoms were nausea/vomiting, headache and weakness. Visual changes, stridor, back and neck pain and visual disturbances were also reported.

CONCLUSIONS: The median diagnostic interval at our unit is below the recommended target of 5 weeks. However, further work is needed to continue to improve awareness of brain tumour symptoms amongst healthcare professionals with an aim of reducing the diagnostic interval to less than 5 weeks for all patients.
Diffuse large b-cell lymphoma of the choroid plexus: a case report

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Primary Central Nervous System Lymphoma (PCNSL) is a rare variant of extranodal non-Hodgkin lymphoma most commonly affecting the eyes, brain, spinal cord and leptomeninges. In the United States, it has a reported incidence of 51 cases per year. Among the subset of PCNSL are tumors arising primarily from the intraventricular regions including the choroid plexus. These cases are extremely rare and on literature review, only four cases have been documented worldwide. This is a case report of a confirmed B-cell lymphoma of the choroid plexus, the first reported case in the Philippines. CASE REPORT. This is a case of a 79-year-old-male with a 2 month-history of continuous headache accompanied by dizziness and seizures manifesting as blank stares and visual hallucinations. He was brought to the hospital with a decreased sensorium and dysarthria; his tongue deviated to the right; and has poor gag reflex. A cranial magnetic resonance imaging displayed enhancing frond-like structures with prominent lobulations in the body, frontal, and occipital horns of both lateral ventricles extending to the third and fourth ventricles with corresponding hydrocephalus. The primary diagnostic consideration on admission was CNS infection. He underwent left frontal burr, endoscopic biopsy of choroid plexus, exudates, and ependyma followed by septostomy and intraventricular lavage; and placement of an Ommaya reservoir. Histologic diagnosis was confirmed to be diffuse large B-cell lymphoma. A repeat cranial MRI, as well as neck, chest, mediastinum, and whole abdominal computed tomography scans showed no other neoplasm. Final diagnosis was diffuse large B-cell lymphoma of the choroid plexus. CSF cytology was negative for atypical cells. Systemic chemotherapy with methotrexate and rituximab was initiated. However, patient already had poor neurological response and the patient’s family eventually decided to put patient on palliative care. Patient was eventually transferred to a smaller hospital facility after being admitted for five weeks.
INTRODUCTION. The use of smartphone apps is an increasing theme for researchers worldwide. MyFitnessPal is a lifestyle app used by c.100 million people. BT-LIFE is a UK Randomised Controlled Trial of lifestyle interventions for fatigue after primary brain tumour, which has been in set-up. We wished to offer patients the option of using MyFitnessPal in BT-LIFE. METHODS. We prospectively surveyed The Brain Tumour Charity's Research Involvement Network of patients and carers. We studied the acceptability of using apps to record lifestyle information in BT-LIFE. Results are summarised descriptively and combined with a frontline narrative of our subsequent experience of sponsorship review. RESULTS. Survey: There were 19 respondents (mean age=49 years [range 31-75]). Of these, 18/19 had a smartphone or tablet which could use apps. Most respondents (16/19) expressed a willingness or preference to use apps, and apps were highly acceptable overall (mean acceptability [n=19] = 8.0 / 10, where 10 is ‘very acceptable’). Narrative: However, the study sponsor was obliged by protocol to query the data protection procedures of the U.S. (non-EU) company that runs MyFitnessPal. That patients would give informed consent, and also have an option not to use the app, were considered irrelevant. The automatic query triggered multiple reviews, in series, that delayed ethical submission by months. This delay jeopardised the study opening date. Accordingly, we removed the app from the protocol. BT-LIFE subsequently opened on-time and is currently recruiting. CONCLUSIONS. Given the acceptability of apps and their ubiquitous use in real life, doing research using apps in the NHS is harder than it should be. Automatically objecting to an app used by millions in daily life may divert governance resources from higher-risk studies, and makes it difficult to do technologically savvy research. We should lobby for ‘common sense’ and streamlined research governance policies that befit modern life.
Early delayed radiation-induced brain injury in mice: preliminary findings using magnetic resonance imaging

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Radiotherapy has improved survival outcomes for central nervous system (CNS) malignancies. However, the negative impact of radiotherapy on the healthy tissue surrounding these malignancies, is increasingly becoming a concern. We aimed to investigate whether the employment of magnetic resonance imaging (MRI) techniques could be used to detect crucial aspects of the time-dependent effects resulting from the exposure of the CNS to ionizing radiation (IR). We hereby report preliminary MRI findings of a study examining the early delayed IR-induced CNS injury in adult CD-1 nude mice that had their right brain hemisphere exposed to a 20 Gy single IR dose by a Small Animal Radiation Research Platform (SARRP). T₂ mapping and multiple b value diffusion weighted imaging (DWI) with a range of observation times of the whole brain were acquired with a 7T small animal preclinical MRI scanner at 6 time-points: before irradiation and then at 1, 10, 17, 60 and 80 days post irradiation. The acquired T₂ mapping data indicated no significant change in actual T₂ values and revealed no significant deviation from normal mono-exponential decay. Similarly, DWI data with short observation times (20-80 ms) showed no significant deviation from Gaussian behaviour, suggesting the existence of no CNS microstructural changes due to IR. However, multiple b value DWI with a 200 ms observation time showed deviations from Gaussian behaviour, suggesting that the assessment of diffusion kurtosis imaging (DKI) could be informative for identifying early delayed radiation-induced brain injury in mice. Our promising MRI findings are examined in parallel with neuropathological observations in the brain tissue of these mice (obtained at 80 days post irradiation), resulting from the assessment of haematoxylin-eosin, cresyl violet, glial fibrillary acidic protein (GFAP) and Luxol fast blue staining in CNS structures of relevance (such as the hippocampus, fimbria, external capsule, thalamus and selected cortical regions).
Effects of dietary lipids on cell viability and stemness in glioblastoma spheroids

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INTRODUCTION: Ketogenic diet may improve glioma patient survival. Nordic populations have low incidences of glioma and typically, a diet high in fish polyunsaturated fatty acids (omega-3 and 6). Gamma-linolenic acid (GLA) is an omega-6 polyunsaturated fatty acid that is converted into prostaglandins PGE1 and PGE2, which have anti- and pro-cancer properties respectively. Altering abundance of PGE1 versus PGE2 via selective inhibition of enzymes involved in GLA metabolism may elucidate the mechanism of GLA anticancer action. Glioblastoma stem-like cells (GSC) are associated with chemoresistance, therefore downregulating stemness genes and promoting GSC differentiation would improve treatment. Previously, peroxisome proliferator-activated receptor (PPAR) agonists such as pioglitazone, have reduced stemness markers SOX and OCT4 by upregulating miRNA145 involved in transcriptional repression. GLA is an agonist at nuclear receptors and transcription factors such as PPAR. The aim of this study was to determine whether GLA in the presence/absence of enzyme inhibitors in the GLA metabolism pathway reduced glioma viability and expression of stemness markers.

METHODS: Cell viability in U87MG and 1321N1 glioma spheroid cultures was measured using the Prestoblue assay following GLA incubation (0-100mM) in the presence/absence of enzyme inhibitors sesamin, cycloate and aspirin. The expression of NANOG and OCT4 was measured by RT-qPCR in GLA treated U87MG and 1321N1 glioma spheroids.

RESULTS AND DISCUSSION: Viability of glioma exposed to GLA were reduced further following COX inhibition by aspirin, suggesting inhibition of prostaglandin synthesis increased apoptosis. Viability appeared to be increased by inhibition of elongase, suggesting GLA in the absence of metabolites may have a tumour protective effect. GLA treatment decreased expression of stemness marker OCT4. Supplementation with GLA and COX-inhibitors to prevent tumourigenic prostaglandins may be a useful adjuvant to standard therapy. Future work will determine if PPAR mediated changes in miRNA expression are implicated in the transcriptional repression of stemness markers.
Glioblastoma (GBM), the most common and aggressive primary brain tumor in adults, remains one of most intractable diseases. Median survival remains at only 15 months, despite aggressive combination therapy involving surgical resection, radiation, and alkylating chemotherapy. While initially responsive to these therapies, GBM tumors quickly adapt and generate treatment-resistant recurrent growths. We and others have previously shown that the stress induced by standard of care therapies itself activates a remarkable plasticity in GBM cells, converting previously differentiated cells to a therapy-resistant glioma stem cell (GSC) state. The exact processes governing this conversion, however, remain to be fully elucidated. Preliminary investigation revealed that polycomb group protein EZH2, a well-established epigenetic regulator, plays a crucial role in this process. To determine how EZH2 responds to therapy, we performed Genome-wide chromatin immunoprecipitation (ChIP) in parallel with DNA sequencing analyses (ChIP-seq), which identified 1449 distinct regions with elevated EZH2 binding, including critical genes PTPRT, CDK5R2, and Siglec6. Microarray analysis demonstrated subsequent attenuation in their gene expression, leading to heightened activity of STAT3, a critical regulator for promotion of the GSC phenotype. To better understand the epigenetic adaptions occurring during therapeutic stress, we performed ChIPseq analysis for histone 3 lysine 27 acetylation (H3K27ac), a marker for active chromatin. Chemotherapy induces H3K27ac enrichment in 452 unique loci, while radiation caused H3K27ac enrichment at 1029 sites. Comparison of these sites to canonical H3K27me3 sites revealed specific de novo binding in the homeobox transcription factor binding motif ($p=0.025$). Combination of our epigenomic data from patient-derived xenograft models and GBM patient data with H3K27me3 enrichment profile allowed us to pinpoint several novel homeobox transcription factors potentially linked to GBM plasticity during therapeutic stress. These results provide critical perspective on the global epigenetic changes driving this plasticity occurring during anti-glioma therapy and provide novel avenues for targeting this adaptation therapeutically.
Evaluation of response to stereotactic radiosurgery in brain metastases using multiparametric MRI

**Poster - E10**

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**BACKGROUND.** Following stereotactic radiosurgery (SRS), brain metastases initially increase in size in up to a third of cases, suggesting treatment failure. Current imaging using structural MRI cannot differentiate between tumour recurrence and SRS-induced changes, creating difficulties with patient management. Combining multiparametric MRI techniques, which assess tissue physiological and metabolic information has shown promise for answering this clinical question. **MATERIALS AND METHODS.** Multiparametric MRI techniques including spectroscopy, diffusion and perfusion imaging were used for differentiation of radiation-induced necrosis and tumour recurrence after SRS for intracranial metastases in six cases. All patients presented with enlargement of the treated lesion, an increase in perilesional brain oedema, and aggravation or appearance of neurological signs and symptoms from 7-29 weeks after primary treatment. **RESULTS.** Multiparametric imaging helped to differentiate features of tumour progression (n=4) from radiation-induced necrosis (n=2). A low apparent diffusion coefficient (ADC) <1000 x 10^-6 mm²/s, high relative cerebral blood volume (rCBV) ratio >2.1, high choline:creatine (Cho:Cr) ratio >1.8 suggested tumour recurrence. A high ADC >1000 x 10^-6 mm²/s, low rCBV ratio <2.1, Cho:Cr ratio <1.8 suggested SRS-induced radiation changes. Multiparametric MRI diagnosis was confirmed by histology or radiological and clinical follow up. **CONCLUSION.** Multiparametric MRI is helpful in the early identification of radiation-induced necrosis and tumour recurrence, which can be used for monitoring treatment changes in intracranial neoplasms after SRS treatment.
Exploring how National Cancer Registry data can be used for the benefit of the brain tumour community.

**Poster - D1**

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1. brainstrust, 2. PHE, 3. brainstrust - the brain cancer people

Brainstrust, the brain cancer people, identified a need, and scope, for an evolving registration service that could develop the conversation about cancer beyond traditional indicators. The All Party Parliamentary Group (APPG) on Cancer too asks for increased data transparency, making more of it available to the public. This must include rare and less common cancers.¹

The aims were to:

- Look at Registry data for a less common cancer (brain) in new ways to address important questions for the brain tumour community.
- Establish a process that can be used by other cancer sites.
- Develop partnership working to make data more meaningful.

**Method**

Stakeholder representatives from the UK brain cancer community attended an initial workshop to:

- Understand the range of cancer registry data available
- Understand how it is currently used
- Define what more it could be doing
- Identify what questions can be asked of the data.

81 questions were identified, of which 42 were potentially answerable using Registry data. Working with PHE, a methodology was developed so that more granular data could be published whilst protecting patient data.

**Results**

Top-level outcomes from this work are:

- The development of the IT interface - it can be done.
- A series of reports which bring data to life.
- Emergent themes from this first statistical release, which need investigating to tell a more informed story.
- Addition of colour to other datasets e.g. early diagnosis.
- Alignment with some of the James Lind Alliance Top Ten Uncertainties².

**Conclusion**

It is possible to provide anonymised population level brain tumour data for public use in the form of standard output tables (http://cancerdata.nhs.uk/standardoutput), in a way that is meaningful for the brain tumour community. This has been a successful, rewarding collaboration between PHE, patients, caregivers, clinicians and brainstrust.

[1] APPG on Cancer Inquiry December 2017
FA-based combinations to target the DNA damage response in glioblastoma.

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BACKGROUND: Despite surgical resection followed by DNA-damaging adjuvant therapies, glioblastoma multiforme (GBM) remains incurable with a median survival of just 15.6 months. Anomalies within the DNA damage response (DDR) contribute to treatment resistance. We have previously shown that the Fanconi Anaemia (FA) pathway, a key DDR process, remains inactive in normal brain but is re-activated in GBM, making it an appealing foundational target for cancer-specific combination therapies.

AIM: To determine whether combined targeting of the FA pathway and interconnected DDR processes could form a basis for new, effective multimodal therapies.

METHODS: Bioinformatic analysis of mRNA expression data (REMBRANDT database) was used to investigate the relevance of FA pathway genes in glioma. Subsequently, immunofluorescence and cell viability assays were used to validate and establish the therapeutic potential of novel FA pathway inhibitors (nFAPi) and inhibition of related DDR targets in established GBM cell models. Finally, combinations targeting the DDR were optimised using immunoblotting, and assessed using clonogenic survival in a novel 3D patient-derived glioblastoma stem cell model.

RESULTS: High expression of downstream FA pathway genes is strongly associated with poor survival (-17.1% 5-year OS, n=329, Log-rank, P<0.0001) and is a feature of more aggressive tumour biology (log2-relative expression, GBM vs WHO Grade I-III gliomas: 7.18±0.02 vs 7.08±0.02, unpaired t-test, P=0.0009). In established GBM models, FAPi and nFAPi were demonstrated to attenuate key markers of FA pathway activity. Of translational importance, nFAPi sensitised GBM cells to temozolomide (comparison of fits F value 63.7, P<0.0001). Inhibitors of PARP1 (PARPi) and ATR also demonstrated potential as temozolomide-sensitising agents. Furthermore, combined FAPi and PARPi significantly reduced cell viability (F value 12.99, P<0.0001) and enhanced radiosensitisation in patient-derived 3D models with sensitiser enhancement ratios (SER0.37) of 1.51 (1.50-1.51, 95% CI) and 1.57 (1.52-1.61), respectively.
Feasibility and utility of arterial spin labelling perfusion in neuro-oncology MRI protocols in the UK.

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PURPOSE: Arterial spin labelling, (ASL) is an MRI perfusion technique that uses endogenous contrast and is currently underused in neuro-oncology MRI protocols in the UK. The purpose of this study was to examine the feasibility, ease of implementation and added value of arterial spin labelling (ASL) perfusion imaging in neuro-oncology protocols. METHODS: Radiographers at a large tertiary MRI centre received in-house training in protocol selection and performing pseudo-continuous ASL (pcASL). During a 10 month period, 104 consecutive patients with gliomas, undergoing diagnostic MRI at 3.0 T, underwent an extended MRI protocol that included pcASL. ASL perfusion weighted images (ASL-PWI) were automatically generated by the scanner and archived together with conventional imaging. A qualitative retrospective survey was performed for feedback on the process. A sub-group of patients with available follow up imaging (n=39) were selected for further analysis (n=39: 20 glioblastoma multiforme, 15 astrocytoma, 4 oligodendroglioma). Two observers examined images and concluded RANO scores in two parts: conventional images alone and conventional imaging with ASL-PWI. Confidence was measured using Likert scales 1-5 (1, very unconfident to 5, very confident) and differences compared. Lastly, all diagnoses were checked against follow up imaging. RESULTS: 90% of radiographers felt either confident or very confident in performing ASL technique. 100% of reviewed PWIs were considered diagnostic quality. A statistically significant increase in average confidence levels was observed for inclusion of ASL (4.44 (SD 0.8)) compared to conventional imaging alone (4.02 (SD 0.65)). CONCLUSION: ASL is a reliable, non-contrast, low cost and well tolerated technique that can be easily implemented. ASL-PWI can be produced at time of scanning which can be utilised to build confidence in assessing response to treatment in low and high grade gliomas.
Glioblastoma in older patients; the impact of the Perry trial on treatment strategies in the UK

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Glioblastoma (GBM) is the commonest primary malignant brain tumour. The average age of diagnosis is 64 years with studies showing survival worsens with increasing age. Part of this may be due to unstandardized treatment regimes amongst the elderly.

There is evidence to support single agent chemotherapy, radiotherapy or concurrent chemoradiotherapy to treat older GBM patients. A recent study published in the NEJM by Perry et al looked at a 40Gy in 15# hypofractionated radiotherapy regime given over 3 weeks with concurrent and 12 months of adjuvant temozolomide. This showed a significant survival advantage of adding temozolomide (greater in those with MGMT methylation) with no change in QoL and potentially established a new treatment paradigm. We investigated current treatment practices in the UK and the impact of the Perry trial.

A cross-sectional survey was performed across all practising UK neuro-oncology consultants with a 60% response rate. 92% of participants mainly see patients post-op rather than performing a pre-op assessment. 89% feel that the publication of the Perry data has changed practice with the majority downgrading their 60Gy/30# CRT regimes to 40Gy/15# in those aged over 70 or with poorer performance status. 92% use the 40Gy/15# regime with 60% using it in up to 50% of their patients. Interestingly 26% of consultants do not have MGMT results available at the time of treatment decisions, mainly due to lab delays. In terms of clinical assessments, only 46% perform routine cognitive assessments and 19% perform frailty assessments on older patients.

There is still a wide variety of treatment regimes used within this patient cohort however the Perry data has been well publicised and instigated a new treatment pathway. More work is needed to explore the clinical basis by which treatment decisions are made and to expedite MGMT methylation testing on a UK wide platform.

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AIMS: Glioblastoma (GBM) is the most frequently diagnosed aggressive primary malignant brain tumour in adults, with a poor prognosis in spite of recent advancements in treatment. Changing treatment paradigms suggest improved outcome, but national data for Wales as a devolved nation has not been reported. The aim of this study is to examine the incidence of patients with glioblastoma in Mid and South Wales and to assess the influence of gender, age, geographical region and treatment on outcome. METHODS: A comprehensive search strategy encompassing all patients coded with GBM and treated between January 2011 and December 2015 was obtained from CaNISC (Cancer Network Information System Cymru), histology reports from University Hospital Wales in Cardiff and Neuro-oncology MDT minutes. RESULTS: There were 512 patients coded with GBM in this 5-year period (57% male, 43% female), giving an overall national age standardized incidence of 5.73/100,000/year. Incidence increases with age up to 70 years, with highest incidence in the 6th decade (median age 66.5 years). Median survival overall was 5.9 months. One, 2 and 5-year survivals in the treated group, were 45.1%, 9.7% and 0.2% respectively. Median survival decreased with increasing age from 14.6 months for the 20–44 year age group, to 7.9 months for the 45–69 years, and 3.1 months for 70+ years. In the maximal treatment subgroup the median survival was 16.1 months. CONCLUSION: Data capture improved over the 5 year period with service development. In spite of higher incidence rates in Wales, the outcomes are comparable to those of England.
Glioblastoma multiforme - search for biomarkers

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Glioblastoma multiforme (GBM) is a rare type of cancer affecting the brain. Despite maximal treatment outcome remains poor with median survival less than two years and devastating effects on quality of life. WHO classification of brain tumours from 2016 added molecular characterization to histological diagnosis that lead to some individualization of treatment. TCGA further classified GBMs in 4 subtypes (mesenchymal, classical, neural, pro-neural) based on genomic analyses with prognostic implications. Tumour microenvironment and the interaction between its components play an important role in GBM aggressiveness. An important way for the intercellular communication for both normal and tumour cells is through the extracellular vesicles (EV's). EV's are lipid bilayer spherical structures that carry a variety of molecules including nucleic acids, proteins, lipids and metabolic products. The release of EV's can be a way of signaling mechanism either locally or systemically and this way it may contribute to tumour progression and resistance mechanism. EVs from GBM cells can be found in biofluids such as peripheral blood, CSF or urine and deciphering their content might provide some inputs in the search for new biomarkers and targets. We studied 6 GBM long established cell lines (LN18, LN229, T98, U87, U118 and U138) for which we were able to assign a specific ‘subtype-like’ signature based on the recently described subtype markers. We observed a correlation between in vitro invasiveness and the GBM subtype tumour cells and their EVs. Mass spectrometry analyses revealed that EVs derived from U87 cells (‘mesenchymal-like signature’) are enriched in protein hits related to GBM progression and neo-angiogenesis, such as CHI3L1 or CD44 pathway mediators (osteopontin, serglycin). Validation studies including patient-derived stem cells in culture but also blood/CSF samples are needed to further decipher GBM cells-derived EVs cargo and find reliable biomarkers.
How effective is the 2 Week Wait (2WW) referral pathway; at detecting patients with CNS tumours; differentiating patients with a tumour from patients without a tumour?

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BACKGROUND: Department of Health Guidelines (DOH) for suspected Central Nervous System (CNS) cancer include 2 week wait (2WW) for specialist consultation, and 62 days from referral and 31 days from decision to treat, to commencing treatment. Currently no guidelines exist for time taken to receive post-specialist imaging; which is the only accurate method of diagnosing a CNS tumour. Large numbers of patients from the pathway do not have cancer; causing an inefficient use of resources. Improving the referral form and communication between primary and secondary care would mean a more effective and specific pathway. AIMS: To assess the use of the current 2WW pathway at University Hospital Birmingham (UHB). Identify reasons for any delays, other routes of presentation, and points at which the pathway could be streamlined. METHODS: Retrospective review of two groups patients at UHB from October 2015 - March 2016. First group were all patients referred to UHB via 2WW, second group were all patients with a CNS cancer diagnosis. RESULTS: Almost half of patients diagnosed with brain and CNS cancer breached the specified timeframes for decision to treat and initiation of treatment. 89% of patients referred via 2WW pathway did not have CNS cancer diagnosis. Of all CNS cancer cases, the majority originated from an external hospital. The commonest symptom recorded by GPs was ‘headache’. DISCUSSION: A surprising number of patients did not meet the DOH guidelines for the CNS cancer pathway, and the majority did not have a CNS cancer diagnosis. Furthermore, there were patients booked into scans by their neurologist that did not follow up their appointments. This creates unnecessary workload in clinics which can be perhaps avoided with a more streamlined referral process. Further research should be carried out to determine the reasons as to why the majority of CNS cancer patients present late.
Identification and validation of novel aptamers for the diagnosis and treatment of oligodendroglioma

Poster - C4

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Oligodendroglioma account for nearly 12% of brain tumours (Jain et al., 2017). In the United Kingdom, 0.4 people per 100,000 per year are newly diagnosed with oligodendroglioma (Crocetti et al., 2012). Early diagnosis and treatment of oligodendroglioma is essential as patients given the appropriate chemotherapy survive on average nearly 8 years longer than patients given radiotherapy alone (Cairncross et al., 2014).

Aptamers are short, single-stranded nucleotide sequences (DNA or RNA) that uniquely fold to form specific recognition molecules that selectively bind to a molecular target. Aptamers against targets are generated using a process called systematic evolution of ligands by exponential enrichment (SELEX). Since 2002, a number of aptamers have been identified that can selectively identify cancerous cells. These aptamers have been used both diagnostically and therapeutically against a range of different cancers, however, there are currently no aptamers specific to glioma tissue.

This first part of this project was to find aptamers specific to the grade IV glioblastoma cell line U87MG. To ensure that highly specific aptamers were identified, a large number of negative controls were utilised, and two variants of the SELEX process were undertaken to ascertain whether the negative controls had to be selected against individually or if they could be pooled.

Patient brain tumour samples have been obtained from the Brain Tumour North West (BTNW) tissue bank and aptamers specific to oligodendroglioma will be selected. These aptamers will be used to screen patient samples to determine if they can identify oligodendroglioma tissue and be of use diagnostically, therapeutically and as a drug delivery tool.
Impact of caveolin-1 in microglial/macrophages and glioblastoma within a tumour environment

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Glioblastoma multiform (GBM) is a highly lethal brain tumour composed by many distinct types of cells that are closely connected and dependent on their surrounding environment. Microglia and macrophages are highly abundant in GBM and create an inflammatory microenvironment that promotes tumour progression. Caveolin-1 (Cav1) is the most important protein of caveolae and is involved in cell signalling activity, regulating the cell proliferation, differentiation and migration. Its role within GBM and microglia/macrophages is poorly understood, so the aim of our project is to investigate how Cav1 status in GBM and microglia/macrophages may modulate the cell-cell communications and the cell invasion.

Three human GBM cell lines (U87MG, UP007 and UP029) and a human microglia cell line (CHME3) were used. Cav1 was knockout (KO) using CRISPR-Cas9 approach. The invasive ability of GBM cells was accessed by 3D spheroid invasion assay. The standard microglial activation was performed with M1 (IFN-γ and LPS) and M2 (IL-4 and IL-13), for 48 hours. Microglia was co-cultured (CC) for 48 hours with GBM cells using Transwell systems. The activation status was accessed by qPCR and WB.

Cav1 KO in GBM prevented the overall spheroid invasion in all GBM cell lines tested. Microglia overexpressed the phosphorylated levels of STAT1 and STAT6 after M1 or M2 polarization, respectively, even when the Cav1 levels were KO. CHME3 Cav1 KO cells seem to be less reactive to M1 and M2 stimulus, decreasing the expression of M1-related markers and some of M2-related markers, compared to Cav1 non-target (NT) cells. The CC of CHME3 Cav1 NT with GBM cells lead to an immunosuppressive environment with a decrease of all M1-related markers and to an up-regulation of TGF-β M2-related marker by the microglial cells.
Improving patient satisfaction: Introduction of a telephone results clinic in Neuro-Oncology follow-up

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**BACKGROUND** It has been shown in one UK centre that telephone clinics helped improve patient satisfaction and lessened the burden on overbooked outpatient services in the low grade glioma setting. **AIMS** We set up a telephone clinic for Neuro-Oncology follow-up patients. We aimed to reduce the burden of patients attending outpatient clinics and improve the follow-up experience for patients who were stable on surveillance imaging. **METHODS** The telephone clinic was offered to selected Neuro-Oncology patients. Only patients stable on standard outpatient follow-up for 12 months and who understood that they may receive bad news over the telephone were eligible. If they were accepting of this and consented to telephone follow-up they were transferred to this clinic. After at least one telephone clinic appointment they were sent a questionnaire to assess their satisfaction. **RESULTS** 34 patient satisfaction questionnaires were sent out to all attendees of the telephone clinic. 26 (76%) responses were received. The respondents were aged 24-74 years and were predominantly male (73%). 24 (92%) had a diagnosis of Glioma and the majority of these were high grade (6 low grade patients: 18 high grade patients). There was a consensus from all patients that the telephone clinic was beneficial to their patient experience. It was found to be a prompt way to deliver information and reduce stress levels, as well as eliminating associated travel time and costs. 100% of patients surveyed preferred telephone clinic appointments to a standard outpatient appointment. **CONCLUSION** From our initial survey, telephone clinics appear to reduce burden on outpatient neuro-oncology services whilst maintaining high levels of patient satisfaction. **REFERENCES** 1) Oberg I, Price S. Nurse-led telephone clinics improve patient satisfaction and enhance follow up for benign/low grade tumour patients. *Neuro-Oncology* 2017. Available: https://academic.oup.com/neuro-oncology/article-abstract/19/suppl_l/i10/3059769 [Accessed 01/02/2018].
Inhibiting Hexokinase 2 implicates a reduction of cell proliferation and drug resistance

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HK2 has a prominent role in aerobic glycolysis and has been implicated in many cancer types including GBM with up-regulation associated with drug resistant phenotypes. Previously, we have demonstrated HK2 over-expression in both GBM biopsy tissue (n=100) and patient derived cell cultures (n=13) through qPCR. A strong correlation with methylation status and overexpression of HK2 was established, with hypomethylation exhibited in all GBM biopsy tissue and cultures via pyrosequencing, The HK2 inhibitor 3-bromopyruvic acid (3-BPA) was shown to induce anti-proliferative effects, and instigate apoptosis in GBM cultures (n=13) under normoxia, with average levels 38% greater in high HK2 expressing cultures (p<0.005). In the present study, we have investigated the response of HK2 inhibitors 3-BPA and metformin in GBM cells grown under hypoxic conditions. Additionally HK2 was knocked out using CRISPR in patient-derived cultures and the established cell line U251MG, to determine change in the rate of cell proliferation and drug sensitivity. Response of GBM cells to both 3-BPA and metformin was significantly lower under hypoxic conditions, with average ID50 values increasing by >20µM for 3-BPA and 20mM for metformin. Average levels of apoptosis (n=8) were diminished under hypoxic conditions from 24.8% to 13.8% in 3-BPA treated cells. A substantial decrease in cell growth was demonstrated in CRISPR modified cultures with an average 43% growth rate reduction after 7 days. Metformin sensitivity was increased in response to HK2 knockout, with average ID50 values 60% lower, in addition 3-BPA revealed a decreased effect with ID50 values 50% higher. This study verifies the significance of HK2 inhibition, implicating the effect upon growth rate and drug resistance. Hypoxic conditions illustrated a reduced response to 3-BPA and metformin inhibition, signifying the importance of further developing HK2 inhibitors that are effective in a significant subset of GBM.
Intensive inpatient neuro-oncology rehabilitation- a new model of care: an evaluation of the first 6 months of this unique service at St. Bartholomew’s hospital

**Poster - D8**

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1. Barts Health

**INTRODUCTION:** Due to advances in cancer treatments, increasing numbers of patients are surviving with brain and spinal tumours. However, patients often have complex neuro-pathology with resulting impairments, and require specialist rehabilitation. With limited in-patient rehab units, patients frequently get stuck in acute settings, reducing patient flow. Alternatively patients are discharged with a high level of dependence and limited rehabilitation potential. A new Neuro-oncology Rehab Service (NORS) was introduced at Barts, in collaboration with Macmillan Cancer Support, to provide intensive neuro-oncology rehabilitation in the acute setting, for 2 years initially.

**AIMS:**

1) To improve patient experience, functional outcomes, and quality of life.
2) To improve patient flow through acute services.
3) To improve links with post-acute rehabilitation services.
4) To enhance patient management by the MDT.

**ACTION:** The service launched in July 2017. A dedicated occupational therapist and physiotherapist were appointed to deliver rehabilitation to patients referred for this service, with dedicated inpatient beds. Within the first 6 months, intensive neuro-rehabilitation was delivered to 25 patients. The service was benchmarked against acute oncology rehabilitation services, post-acute in-patient, and community rehabilitation services. Data were collected and reviewed using outcome measures including the UK FIM+FAM.

**RESULTS:** For all patients who remained under the NORS, improvements were seen in functional outcomes, neurological impairments, quality of life, length of stay, and all patients reported a positive patient experience. The service was well received by the MDT, and there were positive financial implications through reducing patients’ care requirements.

**CONCLUSION:** The service has shown positive early results, meeting its aims. There is potential for this service to be introduced in any acute setting.

**RECOMMENDATIONS:** Thorough data collection and robust analysis should be completed for the remainder of the project term to support service continuation. Data should aim to support formulation of guidelines regarding therapy recommendations for neuro-oncology patients.
Intramedullary spinal cord tumours - a single centre retrospective 10 year analysis

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BACKGROUND. Intramedullary spinal cord tumours are relatively rare tumours of the central nervous system. Surgical outcomes are affected by many variables, including pre-operative neurological function, tumour histology and extent of resection. Emphasis remains on surgical treatment due to the limited adjunctive therapeutic options and poor drug penetration. OBJECTIVE. To identify clinically relevant predictors of progression free survival by retrospectively analysing the anatomical location, pre- and post-operative function and histology in intramedullary spinal cord tumours from a single neurosurgical centre over 10 years. METHODS. 49 patients were identified from a surgical database. Variables collected included pre-and post-operative Frankel Grade and Modified McCormick Scale assessments, tumour histology, extent of resection and length of follow up. Chi-Squared, Kaplan-Mier Survival and Mann-Whitney U-Tests were completed. RESULTS. Ependymoma, Haemangioblastoma and Pilocytic Astrocytoma were the commonest tumour histologies. In total 21 different histological tumours were identified in the series. There was a statistically significant relationship between identification of the tumour plane and extent of resection (p<0.01), along with the extent of resection and recurrence (p<0.01). Compared to the other histological subtypes, ependymoma's demonstrated a significantly greater extent of resection (p=0.02). There was a significant relationship between the grade of tumour and progression free survival (p<0.01). We did not find a significant relationship between pre- and post-operative neurological function and survival. CONCLUSION. Tumour plane and the extent of tumour resection are significant determinants of progression free survival. Ependymoma, whilst being the commonest histology in our series were also the most resectable. Whilst complete resection reduces the rate of recurrence, tumour grade is the most important predictor of outcome.
Investigating the role of TAM family receptors in Merlin deficient tumours

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1. Plymouth University Peninsula Schools of Medicine and Dentistry, 2. University of Portsmouth

BACKGROUND: TAM (TYRO3, Axl and MER) family of receptor tyrosine kinase has been recognised to be upregulated in tumours of diverse origin. Moreover, they are shown to be under negative control of protein merlin, encoded by Neurofibromatosis type II (NF2) gene. Mutation of NF2 gene is responsible for the development of multiple nervous system tumours such as schwannomas, meningiomas and ependymomas. Conventional chemotherapy is ineffective for this group of tumours due to their benign nature, and surgery/radiosurgery carry significant risk due to the multiplicity and location of tumours, thus effective drug therapy is urgently needed.

METHODS: In this study, we are using schwannomas and meningiomas tumour lysates and primary cells to examine the functional and direct correlation of TAM family receptors using confocal microscopy, co-immunoprecipitation and lentivirus based knockdown experiments followed by western blot.

RESULTS AND CONCLUSIONS: Confocal microscopy revealed close association of all three receptors however, co-immunoprecipitation experiments showed direct interaction only between AXL and TYRO3 in schwannomas. Moreover, expression of AXL found to be dependent on TYRO3 and MER. Besides interaction with own members, TAM family receptors also interact with other receptor groups such as integrin β1. Moreover, meningiomas also showed overexpression of all three TAM members in grade-I tumours. Overexpression and activation of TYRO3, AXL and MER found in NF2-/- meningiomas primary cells and which could be reversed on Merlin reintroduction.

Investigating the role of TAM family receptors in pathobiology of schwannoma and meningioma will help to determine the best molecule to target therapeutically for NF2 tumours.
Is it time to radically change the two week wait (2WW) referral pathway for suspected brain and CNS cancer?

Poster - D7

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1. Newcastle University, 2. James Cook University Hospital

BACKGROUND: In June 2015, the National Institute for Health and Care Excellence (NICE) published revised 2WW referral guidelines for general practitioners (GP) for patients with suspected brain and CNS cancer. The guidelines are comprehensive and include recommendations for using brain imaging and provision of relevant clinical information at referral. METHODOLOGY: Retrospective audit of patients referred on 2WW pathway for suspected brain cancer to South Tees Trust between 1/7/2015 and 31/12/2017. Cases were identified from the Trust’s 2WW referral database. Data were collected from referral letters and patient records. Quality of referral information was assessed in 10 domains. RESULTS: 122 patients identified. 98 cases audited (50F:48M, median age 61 years, range 16-92 years). 24 cases excluded: non-brain/CNS 2WW referrals (n=12), spinal cases (n=9), records unavailable (n=3). 54 referrals were rejected as non-compliant under 2WW criteria: 30 with chronic symptoms, 20 with benign lesion/normal brain imaging. Compliance with referral information achieved 100% in 1 domain (patient contact details). Details of past medical history, medications, examination and allergies achieved 56-77% compliance. Details of performance status, social history and patient awareness of referral criteria achieved 2-8% compliance. CONCLUSION: Compliance with the NICE 2WW referral guidelines for brain & CNS cancer is poor. The referral process involves considerable workload for clinical teams especially as 55% of referrals were found to be inappropriate. Compliance may be improved through educational programmes in primary care. Alternatively, by increasing GP access to early cranial imaging, the 2WW pathway could be decommissioned and replaced with a pathway whereby suspected malignancy reported on imaging is linked directly to the neuroscience MDT.
Kent experience with 1st line Temozolamide in elderly patients with High Grade Glioma

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Following publication of two RCT’s demonstrating benefit particularly in those with MGMT methylated (MGMTm) tumours, Temozolomide (T) as an alternative to radiotherapy in elderly patients with Glioblastoma Multiforme (GBM) was adopted as a treatment option in Kent. METHODS: Patients over the age of 60 with new diagnosis of GBM treated with first line T at the Kent Oncology Centre were retrospectively identified from patient records. Baseline demographics, diagnosis details, comorbidity and survival outcomes recorded. RESULTS: Between December 2012 and August 2017 17 patients, median age 72 (range 61-80) commenced T. GBM was histologically confirmed in 59% (10/17), all with MGMT methylation >10% (MGMTm). Diagnosis was radiological in the remainder and MGMT status therefore unknown (MGMTu). 47% had multifocal disease, 52% had significant medical comorbidity and 52% had performance status ≥2. For the whole cohort 13/17 patients have died, MS 9 months (range 1.8-25.5). 5 patients survived over 1 year, 4 of whom had confirmed MGMTm. Median 6.5 cycles (range 1-150) were delivered in those with MGMTm compared to median 3 cycles (range 1-4) in those with radiological diagnosis. 3 patients with MGMTm continue on treatment, median OS 9 months (range 1.9-25.5) in the remainder compared to 1 with radiological diagnosis, median OS 6.7 months (range 1.9 to 11.4 months). CONCLUSIONS Despite significant comorbidity and fitness burdens, the survival outcomes following T in those with MGMTm GBM in our Kent cohort compare favourably to those reported in the NORDIC and NOA-08 trials. Our data supports more limited benefit in those with comorbidity that precludes histological diagnosis and in this situation careful discussion with patients is warranted.
Linear accelerator stereotactic radiosurgery and radiotherapy for multiple brain metastases: outcomes from a tertiary centre

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1. University Hospitals Birmingham NHS Foundation Trust

Stereotactic radiosurgery (SRS) and radiotherapy (SRT) are considered standard of care for patients with 1-3 brain metastases with favourable prognosis. The role of SRS/SRT for multiple metastases remains debated. This project evaluated SRS/SRT outcomes when treating 4 or more brain metastases up to a maximum volume of 20cc. METHODS: Treatment episodes for patients with 4 or more brain metastases were identified from a single centre prospective database from August 2013 to October 2017. All patients were WHO PS 0-1 and treated using Cyberknife. Target volumes were neuroradiology approved with no additional margin beyond the enhancing volume. A retrospective review of electronic records and imaging was undertaken. Overall survival (OS) and distant brain recurrence free survival were calculated using Kaplan-Meier method from the date of treatment, censoring at last clinic visit or MRI respectively. RESULTS: 69 episodes (61 SRS, 7 SRT) were identified with a total of 458 metastases. Primary sites were melanoma (31.9%), lung (29%), breast (27.5%), renal (5.8%), other (5.7%). Median number of targets per episode was 5 (range 4-36). Median SRS dose was 21Gy (range 15-24Gy). Median SRT dose was 24Gy in 3 fractions (range 17.7/3#/27/3#). Median OS was 9.4 months (95% CI 6.5-12.4 months). In patients <65 years median OS was 12.1 months versus 5.9 months for >65 years (p<0.001). Follow up imaging was available for 59 patients and 36 developed new metastases. Median time to distant brain failure was 9.1 months in patients <65 years versus 3 months for patients >65 years (p=0.001). Median OS was 14 months for breast cancer versus 8.4 months for other primary sites (p=0.094). Number of metastases was not predictive of OS or occurrence of distant brain metastases. DISCUSSION: Data supports the ongoing use of volume rather than number of metastases alongside established prognostic factors including age when selecting patients for SRS/SRT.
Neuro-oncology patients should have access to a tumour-site-specific “Health & Wellbeing” workshop

Poster - D4

Ms. Victoria Hurwitz ¹, Mr. Ranj Bhangoo ¹, Mr. Keyoumars Ashkan ¹, Mr. Francesco Vergani ¹, Dr. Lucy Brazil ², Ms. Jessica La ¹, Ms. Laura Mullens ¹, Dr. Angela Swampillai ², Dr. Katia Cikurel ¹, Ms. Nicola Peat ², Dr. Bali Rooprai ¹, Dr. Gerald Finnerty ³

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Introduction: The figures for neuro-oncology patients attending “Health & Wellbeing” events are submitted to the cancer registry on a quarterly basis. The number returned has been zero since records started. One reason patients give for not attending generic cancer events is that they feel the events would not be relevant to them. Studies of patient experience reveal a major gap in their care pathway: patients require support and information on how to cope with the symptoms caused by their tumour and the side effects of treatment and medication. Method: The Brain Tumour Charity (BTC) wrote a report “Losing myself – the reality of life with a brain tumour” based on a patient questionnaire. This report formed the basis of planning the day’s programme. Neuro-oncology patients who have had surgery, radiotherapy or chemotherapy and their carers were invited to attend the event. The agenda focused on the key areas highlighted in the BTC report, namely: fatigue; emotional control; and living with the threat of disease. Results: Nine patients and three carers attended the first workshop. 100% of the attendees would recommend the event to a friend or family member. Over 66% of attendees will be making changes to their life based on what they learnt from the event, such as “more understanding of my partner and look after myself better as a carer” and “using the things I learned today to make me feel more like my old self”. Conclusion: Neuro-oncology patients who have been treated would benefit from access to a tumour-site-specific event that focuses on helping them to improve their well-being. What was the best part of the day? “all of it – super informative and a very friendly atmosphere that makes me feel much less lonely in all of this".
Neurosurgical management of brain metastases: outcomes and trends from a major neurosurgical centre

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Nottingham University Hospitals NHS Trust (NUH) - a large neurosurgical centre serving 3.2 million patients - has seen a large increase in referrals to its neuro-oncology multidisciplinary team meeting (MDT) for patients with brain metastases. Consequently, a separate MDT has been formed to meet the demand. In general, patients who are selected for surgery are those with neurological symptoms that would be relieved by tumour resection and who are also not suitable for stereotactic radiosurgery (SRS). Furthermore, these patients need to have a life expectancy of greater than six months, good primary disease control and a performance status score of one or two in order for the benefits of surgery to outweigh the risks. We retrospectively reviewed patients selected for neurosurgical intervention between September 2016 and September 2017. 43 patients were identified. The six month survival rate was 62.97%. After preliminary qualitative analysis we identified two recurring themes potentially affecting patient outcomes. Firstly, in many cases where post-operative MRI to detect residual tumour was equivocal, subsequent decisions to withhold post-operative adjuvant therapy later lead to disease recurrence at the surgical site. Notably, we found poor correlation between the intra-operative perception of complete tumour resection and the subsequent post-operative MRI, which often identified residual tumour. Secondly, the practicalities of complex patient cases meant MDT outcomes often took several weeks. This at times lead to changes in patient care. For example, in some cases the decision for SRS had to be revised as increased tumour size made SRS no longer favourable. Due to these many intricacies, neurosurgical centres may benefit from separate brain metastases MDTs, such as seen at NUH. Further quantitative research is needed to investigate the impact of the perceived complete resection of brain metastases on subsequent management decisions.
Optimising the 3D Hi-Spot culture model for glioblastoma.

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1. Cardiff University

Chemotherapeutic options for glioblastoma (GBM) are limited, which contributes to the poor prognosis. Established cell lines have many phenotypic differences from their original tumours, and drugs which show success in animal models often fail to translate to humans. We aim to expand our previous work in growing Hi-Spots from human brain tissue to provide a representative 3D *in vitro* model of GBM using *ex vivo* human tumour samples, on which drug candidates can be tested. Hi-Spots are a high-density 3D cell culture technique. Cancer and microenvironment cells are mechanically and enzymatically isolated from fresh resected or biopsied tumours, seeded onto PTFE membranes and cultured on an air-liquid interface. The Hi-Spot medium has a high serum content to support initial cell survival. Serum was either fully or partially removed at 7 DIV (days in vitro), and cell cycle kinetics were studied by EdU incorporation and Ki67 immunocytochemistry. Cultures were stained for beta-III tubulin (TUJ1), glial fibrillary acidic protein (GFAP) and nestin to identify expression of neuronal, astrocytic, and neural stem cell markers. Cells positive for TUJ1, GFAP and nestin (commonly expressed by GBMs), represented 26%, 8% and 31% of cultures, respectively, with some overlap. After an initial decrease, cell numbers are stable from 7-14 DIV, then decrease further. Cell proliferation is highest between 7-12 DIV. Cultures which are switched to a serum-free media at 7DIV survive better and maintain a higher fraction of Ki-67+ cells up to 21 DIV. Switching to a serum-free media at 7 DIV maintains the cultures for longer, so this will become the standard protocol. The stable window between 7-12 DIV may be optimal for future investigations, when the cultures best replicate the original tumour. This work suggests Hi-Spots allow for culture of human GBM cells, and have potential as a model for future drug testing.
Pineal parenchymal tumour of intermediate differentiation (PPTID): Excellent response to treatment leads to an unexpected complication.

BACKGROUND: PPTID is a rare tumour of the central nervous system, in a spectrum between pineocytoma and pineoblastoma. Case series have indicated that after sub-total resection radiotherapy is associated with better survival. CASE: A 66 year old lady presented to A&E with collapse after a six month history of headache, poor balance and decreasing mobility. Imaging revealed a 5x4cm enhancing lesion in the pineal gland, hydrocephalus and widespread leptomeningeal seeding around brainstem and spinal cord. She underwent a stealth guided biopsy and ventriculo-peritoneal (V-P) shunt insertion. Histology demonstrated a grade 3 PPTID, Ki-67 30%. Further surgery was not undertaken due to the widespread disease and craniospinal radiotherapy was felt too toxic given her poor performance status. Therefore, she received palliative radiation to the bulky intracranial disease. MRI brain post treatment demonstrated an excellent response. One year later she presented with spinal cord compression, necessitating radiotherapy, during which she became acutely drowsy and confused. CT head revealed widespread pneumocephalus and a bony defect in the sphenoid sinus in continuity with the CSF space. Reassessment of her initial scans identified bony erosion by disease near the superior aspect of the left sphenoid sinus. On current imaging this tumour focus had resolved. Additionally the V-P shunt was producing a modest negative pressure so we hypothesised that the excellent response to radiotherapy had removed the tumour plug and allowed the pneumocephalus to occur. The patient underwent a joint ENT/neurosurgical procedure to seal the bony defect and this, in conjunction with ligation of the shunt, resulted in resolution of both imaging findings and the patient's symptoms. CONCLUSION: In radiosensitive disease we must consider the consequences of the tumour itself, but also complications that may arise on tumour regression.
Pineal region glioblastoma: report of two long term survivors

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1. James Cook University Hospital

**BACKGROUND:** Pineal region glioblastoma (GBM) is an rare entity and is considered to have a poor prognosis similar to cerebral GBM. The current literature describes approximately 28 cases of pineal region GBM reported worldwide with no case series of more than 3 patients. Even with radical treatment the median survival is reported as 6 months (range 6-24 months) with occasional reports describing survival in the range of 24-38 months.

**METHODOLOGY:** Retrospective audit of all cases of GBM treated in our unit between 2008 and 2018. Data were collected from pathology reports, case notes, clinic letters and MDT outcomes.

**RESULTS:** We identified only two cases of pineal region GBM in male patients, aged 21 years and 50 years at the time of diagnosis (in 2013 and 2011 respectively), who are alive at 53 and 75 months since diagnosis. They are still under follow-up, maintaining a good performance status with no radiological evidence of tumour recurrence till date. Both patients had a biopsy, CSF diversion procedure, radical radiotherapy with concomitant temozolomide chemotherapy and 6 cycles of adjuvant temozolomide.

**CONCLUSION:** Although the overall survival for GBM following only a biopsy and chemoradiotherapy is considered poor, our experience of these tumours in the pineal region show a longer survival with similar treatment, when compared to GBM in cortical location. A larger study including detailed molecular genetic analysis may help in better understanding of the tumour behaviour and whether the location in the pineal region may be of prognostic value. Due to the rarity of GBM in the pineal region, this may only be possible if multiple centres collaborate in such studies.
Post-operative fractionated stereotactic radiosurgery (fSRS) to the resection cavity of brain metastases – a single institution review.

INTRODUCTION: In the post-operative setting, fractionated stereotactic radiosurgery (fSRS) is increasingly used as an alternative to whole brain radiotherapy (WBRT) for brain metastases. Retrospective cohort studies have shown comparable survival and similar local and distant control, with some avoidance of neuro-cognitive decline. This review looked at patients treated with fSRS for this indication at our institution.

METHODS: We performed a retrospective review of patients (N=18) who received fSRS to their post-operative cavity for an isolated brain metastasis between 1 January 2016 and 31 December 2017. The median follow up was 8.1 months [2.8-17.1]. The primary endpoints were Overall Survival (OS) and Relapse Free Survival (RFS). Relapse was considered as: recurrence at the treated site; new disease at another intracranial site; or progression at an extracranial site. There were seven different primary tumour sites.

RESULTS: All 18 patients received 30 Gy in five fractions over 10-14 days. The median target volume was 18.5 cc [2.31-45.47] and the mean equivalent sphere diameter was 3.1 cm [1.6-4.4]. OS at 3, 6 and 12 months was 94.4%, 76.4% and 65.5% respectively and the median OS had not been reached at time of data analysis. RFS at 3, 6 and 12 months was 88.9%, 46.7% and 26.7% respectively, with a median RFS of 6 months. There were no reports of radionecrosis or severe (>grade 2) toxicity.

CONCLUSIONS: At our institution, post-operative fSRS with 30 Gy in five fractions for surgically resected brain metastases was well tolerated and achieved good local control. These results compare well with those historically seen with WBRT. We await the recently proposed ESTRON study and will continue to review our local results.
Radiomic evaluation of treatment response in patients with glioblastoma: a pilot study

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BACKGROUND. Pseudoprogression of glioblastoma multiforme (GBM) following treatment occurs in 33-64% of patients. Conventional MRI cannot distinguish between pseudoprogression (psPD) and true tumour progression (tPD). Radiomic features could be used as predictors of treatment response. Our aim is to identify radiomic features that can be used to distinguish between psPD and tPD in patients with GBM. MATERIALS AND METHODS. For this pilot study, we retrospectively analysed 20 MRI studies of patients with biopsy-proven GBM. Those who developed early progressive enhancing disease (ePD) at 4-6 weeks following standard chemo-radiotherapy (CRT) treatment with temozolomide were included. Studies were labelled tPD or psPD from results of the follow-up scan at 6-months post-CRT. Tumour components on post-contrast T1W and T2W axial sequences were semi-automatically segmented under the supervision of an experienced radiologist using ITK-SNAP for enhancing disease and oedema respectively. Radiomic grey-level co-occurrence matrix (GLCM) textures were calculated using CaPTK. Statistical analysis was performed to determine the significance between means of both groups.

RESULTS. A total of 20 patients with 11 tPD (3 female, 8 male) and 9 psPD (7 female, 2 male) were included in this study. There were significant differences in the texture features of contrast, homogeneity, grey level non-uniformity (GLNU) and run-length non-uniformity (RLNU) between the tPD and psPD groups within the enhancing disease on post-contrast T1W imaging. RLNU, GLNU and the overall volume showed significant differences between both groups on analysis of oedema on T2W imaging. CONCLUSION. In our pilot study, the limited GLCM texture features extracted from standard post-contrast T1W and T2W images showed significant differences between the tPD and psPD groups on the first follow up scan following CRT. With further validation through larger studies, these could prove to be useful radiomic and radiogenomic features for earlier prediction of treatment response and prognosis.
Retrospective single centre review of temozolomide (TMZ) vs procarbazine, carboplatin, vincristine (PCV) chemotherapy in patients with glioblastoma (GBM) WHO grade IV at first relapse following treatment with the Stupp protocol.

**Poster - C5**

**Dr. Nicola Davis**, **Ms. Kathryn Innes**, **Ms. Laura Mullens**, **Ms. Victoria Hurwitz**, **Ms. Jessica La**, **Mr. Ranj Bhangoo**, **Mr. Keyoumars Ashkan**, **Dr. Ronald Beaney**, **Dr. Lucy Brazil**, **Dr. Angela Swampillai**

1. Guys and St Thomas NHS Foundation trust, 2. King’s College Hospital NHS Trust, 3. Guy’s and St Thomas Foundation NHS Trust, 4. Guy’s and St Thomas NHS Foundation Trust

**PURPOSE:** The standards of care for patients with a GBM at relapse are not well defined. We sought to establish details of the treatment given to patients at initial relapse, and information about outcomes (PFS, OS) in our patient population in a large regional neuro-oncology centre. The aim was to establish whether rechallenge with TMZ is beneficial over standard second line PCV based treatment.  

**METHODS:** Retrospective single centre review of medical records of patients with Grade IV GBM who received Stupp protocol treatment at Guy’s Oncology Centre from 2011-2017. Information was obtained on their initial diagnosis (including molecular profiling), details of treatment, time to first relapse, subsequent treatment received, time to further progression and overall survival.  

**RESULTS:** Complete analysis of data from over 200 patients are awaited.  

**CONCLUSION:** although the BR12 trial compared PCV to TMZ in first relapse this was in chemo-naive patients. Therefore in the post Stupp era, and with the benefit of molecular profiling data, data from our review of clinical practice will guide chemotherapy treatment of first relapse in GBM patients.
Segmentation of brain tumor in fluid-attenuated inversion recovery magnetic resonance imaging by gray-level occurrence matrix and extreme learning machine

Poster - B8

Dr. Shui-hua Wang ¹, Prof. Yuxiu Sui ², Dr. Yudong Zhang ³

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AIM) Tumor segmentation is one of the most challenging tasks due to the unpredictable appearance and shape. Our team proposed a computer-vision based approach for segmentation of brain tumors, including tumor core and peritumoral edema. (METHOD) We used fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). In total our cohort consists of 20 patients, with 10 low-grade gliomas and 10 high-grade gliomas. Three neuro-radiologists with experiences over ten years were invited to delineate the tumor regions. Sliding neighborhood processing (SNP) was used to generate image-patch samples. Since non-tumor samples are significantly larger than tumor samples, the cost-sensitive technique was used to sort out this class-imbalanced problem. Gray-level cooccurrence matrix (GLCM) was used to extract features. The extreme learning machine (ELM) is a feedforward neural network where the parameters of hidden nodes need not be tuned. ELM usually can be trained within one single step. In this study, ELM was used as the classifier, predicting each pixel tumor or non-tumor. A 10-fold cross validation was used to report the out-of-sample performance. (RESULT) Suppose the tumor pixel is true class, and non-tumor pixel is false class. The experiment results showed our method achieved a sensitivity of 83.61%, a specificity of 84.74%, and an accuracy of 84.17%. (CONCLUSION) The results are competent to expert delineation. In addition, this proposed method is fully automatic and reproducible. Our method is promising in assisting neuro-radiologists in delineate tumor regions.
Stacked In-plane Histology for Quantitative MRI Assessment: Application to An infiltrative Brain Tumour Model

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Introduction: To improve the validation of Non-invasive imaging techniques (e.g. Magnetic Resonance Imaging, MRI), we have developed a pipeline whereby stacked in-plane histological sections which can be used for quantitative assessment. This allows for a quantitative voxel-by-voxel assessment, give correlates against the gold standard histology.

METHOD: Ten nude mice were injected intracranial with (G7 Glioblastoma model 5x10⁵ cells per mouse). Immediately following MRI scanning (T1w, T2w, DWI, and ADC) the mice were sacrificed and the brains removed and fresh frozen. After that, sections were stained for Human Antigen Leukocyte (HLA) and hematoxylin and eosin (H&E). Three histological sections were selected to create a Tumour Cells Density (TCD) map, which was co-registration with a multi contrast MRI dataset, to create a 3D matrix. Results: All imaging techniques exhibited very high Dice coefficient (>0.8) with histology, characteristic of an excellent segmentation. There is statistical significant between TCD and MRI techniques, however, no statistic significant between MRI and each individual histology section alone. Therefore, using one section may led to misconception. In addition, ROC curve analysis shows that TCD matches tumour volume better than for one section.

Conclusion: We present a pipeline whereby stacked in-plane histological sections is used to create a TCD which can then be co-registered with MR images. This allows direct validation by voxel-by-voxel comparison, allowing for direct quantitative validation of new MRI methods.
Support group for newly diagnosed patients with brain tumours

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1. King’s College Hospital NHS Trust, 2. King, 3. guys and st thomas foundation trust

Kings College Hospital Neuro-oncology have struggled to maintain support group numbers. We have observed that patients/carers usually attend once, at the time of diagnosis and are typically angry, asking ‘why me?’ Core members reported that they felt ‘brought down’ by new attenders displaying anger and felt a ‘pressure to pick them up.’ Group facilitators observed patients this dynamic unintentionally created a barrier for group involvement. An additional support group therefore has been trialled; ‘New diagnosis and what to expect next.’ Two of the new group meetings have run to date: 35 attenders in November 2017 and 15 attenders in March 2018. The group session is led by a Clinical Nurse Specialist and a specially trained Psychotherapist (Dimbleby Cancer Care) and split into the following facilitated group discussions:

• How were you diagnosed?
• Typical diagnostic pathways
• Current Emotions
• What to expect next
• Rehabilitation

The following feedback has been collected to ensure the structure of the support group is meeting the needs of this patient population and will improve where necessary.

‘What was great was the opportunity to meet other people who are in a similar position to myself.’

‘It has really helped me to be easier and more forgiving with myself, to know fatigue is normal and I’m not just being lazy!’

‘It was great to meet other patients with similar conditions.’

‘It would have been great to have more time to just talk to other people in the group without being in a “circle”. It would be really useful to add to the session some of the key things that would can help me such as covering travel costs, prescription costs etc.’

Further groups sessions will be adapted to meet these and more responses and build on this service with ongoing evaluations.
Systematic review and meta-analysis: arterial spin labelling (ASL) efficiency in grading of adults glioma

Ms. Amirah Alsaedi 1, Dr. Fabio Martino Doniselli 2, Prof. Sotirios Bisdas 1, Prof. Xavier Golay 1

1. UCL, 2. University of Milan

Through a systematic review, the research quantitatively evaluates the efficiency of arterial spin labelling (ASL) in identifying glioma grades. EMBASE and MEDLINE were consulted, and 18 studies were selected. In turn, quantitative data were gathered, and a meta-analysis conducted. 8 included studies published CBF values as a mean and SD; 3 published cut-off values and sensitivity/specificity levels; while the remainder addressed both. Tumour blood flow (TBF) references were different, and so were renamed as follows: the TBF was denoted the mean (TBFmean/rTBFmean); the ROI incorporated the whole tumour; or the ROI was chosen with standard images (e.g., T2W). The identified ROI for the perfusion map’s high signal was denoted the maximum (TBFmax/rTBFmax). QUADAS-2 was used for quality appraisal, while statistical analysis was divided as follows: firstly, a random-effects model and a forest plot; and secondly, a system modelling specificity and sensitivity outcomes (owing to the inverse relationship that links them), paired with a hierarchical summary receiver operating characteristic (HROC) curve. The absolute TBF displayed the power to distinguish between HGG and LGG, along with grade-II from grade-IV. Nevertheless, it could not distinguish between grade-II and grade-III or grade-III and grade-IV. Contrastingly, rTBFmax was more effective in glioma grading. An identical outcome was derived from sensitivity and specificity analysis, with rTBFmax showing the highest levels for glioma grading. Estimated effect size for rTBF was compatible to HGG and LGG, as well as grade-II and grade-II ((-1.46, (-2.00, -0.91)), (-1.39, (-1.89, -0.89)), respectively; however, between grade-III and grade-IV, the effect size was reduced (-1.05, (-1.82, -0.27)). This result also derived from the sensitivity and specificity analysis, where ASL demonstrated greater sensitivity when distinguishing between grade-II and grade-III than between grade-III and grade-IV. It follows that ALS is effective for glioma grading when perfusion values show significant differences between glioma grades, especially rTBFmax.
The challenges of treating a high grade glioma in a pregnant patient

Poster - C9

Dr. Priyanka Patel ¹, Dr. Ronald Beaney ², Dr. Angela Swampillai ², Prof. Keyoumars Ashkan ³, Mr. Ranj Bhangoo ³, Ms. Laura Mullens ³, Ms. Victoria Hurwitz ³, Dr. Lucy Brazil ²

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Glioblastoma diagnosis carries a poor prognosis. A combination of surgical resection and chemo-radiotherapy is the current standard of care with median survival rates of 15 months. A 33 year old lady, pregnant at 26 + 3 weeks gestation presented with a left parietal tumour. Complete resection confirmed a grade IV glioblastoma. Foetal health remained stable and termination was not considered. The patient attended for discussion on adjuvant treatments and was informed of the time critical nature of radiotherapy; temozolomide was not advised during pregnancy. With the patient understanding the increased risks to the foetus, the radiotherapy process for delivering 60Gy/30 fractions was initiated. Standard radiotherapy plans were created using both VMAT and 3D-CRT technique. At the planning CT fiducials were placed at the xiphersternum to represent the maximum superior foetal extent and measurements taken. Using a phantom and TLDs, an estimated dose to the foetus was 30mGy from a VMAT plan and 20mGy from 3-field 3DCRT, assuming a 0.5mm equivalent lead apron. The effects to the foetus were calculated using the Health Protection Agency document RCE-9. Radiotherapy increased the incidence of childhood cancer from 1/500 to 1/250. Additional risk of inheritable effects was (1/6700) and deterministic effects was below the threshold. The increased dose of 10mGy from 3DCRT to VMAT plan meant the additional risk of childhood cancer increased from 1/625 to 1/400. Although considered safe, the patient decided against radiotherapy until after delivery at 32 weeks. We will also present a case of a patient diagnosed with a frontal anaplastic astrocytoma at 19 weeks gestation. The patient consented to go ahead with radiotherapy with similar foetal radiation doses. Considering the health of the foetus and mother brings a unique challenge when planning the management of high grade gliomas.
The Neurosurgical Admissions pro-forma

Dr. Sameera Sharma ¹, Mr. Christopher Cowie ¹
¹ Newcastle University

The quality of admissions documentation and examination is directly linked with patient care. The objective of this quality improvement project (QIP) was to assess and improve the standard of admissions documentation in the Neurosurgery department at Royal Victoria Infirmary, Newcastle upon Tyne. In comparison with the Royal college of Surgeons (RCS) guidelines published in 2015, the standard of admissions documentation and examination in Neurosurgery were sub-optimal. This was attributed to the lack of a standardised admissions pro-forma.

We formulated a four page admissions pro-forma based on the RCS guidelines assessing 27 of the 32 criteria addressed in the guideline. We introduced the format of the pro-forma to the junior doctors and made it available for use in all emergency admissions wards. Based on the uptake of the pro-forma, we then scrutinised case notes of 20 patients where 10 had been clerked using free hand method and 10 using the pro-forma.

There was significant improvement in the quality and standard of admissions documentation with the use of the pro-forma. In addition, adherence to RCS guidelines increased from 45% with free hand clerking to 85% with the use of a pro-forma. Moreover, with the introduction of this pro-forma, Standardisation of the structure and content of admissions documentation was made possible.

Our recommendations were accepted and the pro-forma has become an integral part of emergency Neurosurgical admissions documentation. In order to increase uptake and to acquaint new doctors to the pro-forma, an introductory presentation will take place during every departmental induction. In addition, to increase awareness among doctors, of the standard of documentation expected of them, posters of a filled pro-forma will be displayed in every Neurosurgical wards.
Treating high-grade glioma (HGG) in the elderly: has anything changed?

Ms. Anna Solth, Mr. Jing Xian Lee, Mr. Gareth Dobson, Mr. Nitin Mukerji, Mr. Anil Varma, Prof. Philip Kane

James Cook University Hospital, Newcastle University

Following a previous review of our experience managing HGG and finding that carefully selected elderly (age ≥65 years) patients benefit from radical treatment we decided to re-audit our practice.

This retrospective audit concerns patients with a histological or radiological diagnosis of HGG over four non-consecutive years, 2011 onwards. Patients were identified via the trust cancer management systems. Survival data was calculated for patients presenting in 2011, 2013 & 2015.

147 patients were identified, 71 of them elderly. The overall median age was 64 years.

In 2011 23 patients presented to the MDT (39% of which were elderly), 44 in 2013 (52% elderly), 31 in 2015 (52% elderly) and 49 in 2017 (47% elderly). The median age of the elderly patient group was 67 in 2011, 72 in 2013, 70 in 2015 and 72 in 2017.

Most patients underwent debulking +/- adjuvant radio-chemotherapy: 74% of the younger and 66% of the older patients. The median survival was 12 months for younger and 5 months for older patients. Patients who had debulking surgery +/-adjuvant radio-chemotherapy had a 13 and 6 months survival, respectively.

Although the percentage of elderly patients referred to the MDT did not increase, the median age of the elderly patient group has increased over the years. Two thirds of elderly patients received aggressive treatment, which was unchanged to our practice in 2007. Median survival times for HGG did not improve compared to our previous audit.

Performance status at presentation may be an important factor in patient selection but better measurements of “frailty” in the elderly population are required to assist in management decisions.


Variable RNA sequencing depth impacts gene signatures and target compound robustness – case study examining brain tumour (glioma) disease progression

Poster - A10

Dr. Alexey Stupnikov, Dr. Caitríona McInerney, Dr. Paul O’reilly, Mrs. Aideen Roddy, Dr. Philip Dunne, Mr. Alan Gilmore, Dr. Hayley Ellis, Mr. Tom Flannery, Dr. Estelle Healy, Dr. Stuart McIntosh, Dr. Kieran Savage, Prof. Manuel Salto-Tellez, Dr. Frank Emmert-streib, Dr. Kathreena Kurian, Prof. Kevin Prise, Dr. Darragh McArt

1. Johns Hopkins University, 2. Queen’s University Belfast, 3. University of Bristol, 4. Belfast Trust, NHS, 5. Tampere University of Technology

Available treatments for glioma have limited effectiveness rendering this a disease of poor clinical outcome. Gene expression profiling can uncover the biological mechanisms underlying disease, information that is crucial for drug development or repurposing. RNA sequencing (RNA-seq) is routinely used to assess gene expression but costs remain high. Whilst sample multiplexing reduces RNA-seq costs, the lowered cDNA sequencing depth of multiplexed samples may hinder accurate differential gene expression detection. The impact of sequencing depth alteration on RNA-seq-based downstream analyses such as gene expression connectivity mapping is not known. Connectivity mapping is a method used to identify potential therapeutic compounds for drug repurposing. In this study, published RNA-seq from brain tumour (glioma) patients were analysed and assembled into two gene signature contrasts for astrocytoma disease progression (WHO Grade II-III; III-IV). Gene signatures were subsampled to simulate sequencing depth alterations and analysed in connectivity mapping to investigate target compound robustness. Data loss to gene signatures led to the loss, gain and consistent identification of significant connections to target compounds. The most accurate gene signature contrast with consistent patient gene expression profiles was more resilient to data loss and identified robust target compounds. Target compounds lost included candidate compounds of potential clinical utility in glioma (e.g. Suramin, Dasatinib). Lost connections may have been linked to low abundance genes in the gene signature that closely characterised the disease phenotype. Consistently identified connections may have related to highly expressed abundant genes that were ever-present in gene signatures, despite data reductions. Potential noise surrounding findings included false positive connections that were gained as a result of gene signature modification with data loss. Findings highlight the necessity for gene signature accuracy for connectivity mapping, which should improve the clinical utility of future target compounds identified for drug repurposing.
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