axis. This episode was again managed by a course of steroids and oral antibiotics. Since Temozolomide was the optimal treatment to control the disease progression at this stage, we agreed to persevere with temozolomide using a rapid desensitisation protocol. RESULTS: On the first day of third cycle, she was brought to the day chemotherapy unit and given prednisolone 30mg, fexofenadine 180mg and ondansetron 8mg, 30 minutes before the treatment. Our protocol was as follows; 5mg, 10mg, 20mg, 30mg, 50mg and 90mg of temozolomide at an interval of 30 minutes between the doses. She was advised to follow the same regime for the next four days of the third cycle. On days 6 -28, she has been advised to take fexofenadine 180mg once daily. Although there was a minor rash appeared on days 6/7, they subsided gradually. She tolerated the treatment without sinister symptoms or signs. We proceeded with the next 4 chemotherapy cycles adhering to the same protocol. The intensity of the rash gradually improved, and she became almost completely asymptomatic by the 7th cycle. It was also encouraging to see the radiological response of the tumour with the treatment. CONCLUSION: Although the published literature is minimal, rapid desensitisation is shown to be a safe and effective method to counteract temozolomide hypersensitivity. In an era where there is still a paucity of systemic treatment options for primary brain tumours, adopting rapid desensitisation to induce tolerability to temozolomide, a drug which has shown to improve survival, would be a valuable addition in managing our patients. Further, our experience suggests that this protocol is safe, effective, and does not necessitate inpatient admission.

URGENT ELECTIVE PATHWAY SERVICE RECONFIGURATION FACILITATES INCREASED USE OF SURGICAL ADJUNCTS, IMPROVEMENT IN SURVIVAL TRENDS, AND REDUCED HOSPITAL STAY FOR GLIOBLASTOMA PATIENTS

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AIMS: Glioblastomas (GB) are the most common and aggressive of intrinsic brain tumours. Median survival with maximal therapy is reported to be 14.6 months. Service reconfiguration at the Queen Elizabeth Hospital Birmingham (QEHB) has transformed the service for high grade brain cancer patients, including GB, from a predominantly emergency pathway based system to one of planned urgent-elective admissions consisting of: A. Patient-focused, consultant-led, research orientated "one stop shop" model of integrated outpatient neurosurgical oncology clinic B. Standardisation of urgent elective pathways C. Incorporation of neuro-surgical intra-operative adjuncts (neuro-monitoring, 5-ALA) into routine surgical practice for oncology. Using this model, we have reduced hospital length of stay (with associated financial savings), improved extent of resection and achieved a trend towards increased survival. METHOD: We retrospectively identified patients with primary histological diagnoses of GB (WHO grade IV), who underwent surgery over a six year period, from 01/01/2014 to 31/12/2019, from the QEHB pathology database. Data was collected for demographics, surgical and oncological therapy, use of intra-operative adjuncts, emergency and elective admission status, year of admission, length of stay (LOS), and extent of resection (EOR) on first post-operative MRI scan from hospital databases. Survival was analysed using the Kaplan-Meier method and independent-samples median testing for survival. Proportion of patients undergoing resective surgery and admission status was calculated by year. Overall median survival was calculated and subgroup comparisons made of patients by: age, admission status, year of admission, biopsy or resection, oncology treatment. Hospital length of stay was calculated for patients by surgical procedure, admission pathways and compared across the year. Financial data taken from averages of inpatient episode costs were used to estimate cost savings. RESULTS: 610 patients underwent primary procedures for GB, of which 64 were still alive at time of analysis (02/02/2021). Median overall survival time was 9.53 months, this was greatest in patients who underwent resection with completion of Stupp protocol: 28.67 months (n=114). From 2014 to 2019, there has been an increase in elective admission rates (28.1% to 90.3%, $p<0.001$) and increased proportion of resective surgery (68.4% to 81.9%, $p<0.001$). There is a trend of improved survival from 2014 to 2019 (median 7.95 and 11.08 months, $\chi2=9.249$, $p=0.002$). Increasing use of intra-operative adjuvants improved EOR ($\chi2 =31.064$, $p<0.001$). Through improved urgent-elective admission rates, hospital length of stay has decreased by five days for craniotomies and six days for biopsies. Cost analysis of three cases demonstrated that reducing the LOS by one night alone result in an average cost saving of approximately £750 per patient per night. CONCLUSION: Switching to a system of planned and urgent elective based admission, with standardisation of neuro-oncology patient pathways, increased use of intra-operative adjuncts, earlier oncology multidisciplinary input and outpatient review, has improved the extent of GB resection, led to shorter length of hospital stay associated with significant financial savings and achieved a trend towards increased overall survival.

EXTENT OF RESECTION IN GLIOBLASTOMA: A 10-YEAR LOCAL SURVIVAL ANALYSIS

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AIMS: The impact on extent of resection (EOR) in glioblastoma has been well documented. It is clear that gross-total resection (GTR) confers best overall survival (OS), however the minimum EOR required to confer a survival benefit over biopsy is debated. Recent studies favour partial resection (PR) over biopsy for IDH-wildtype, MGMT-unmethylated tumours. We describe our experiences locally with these principles in mind. METHOD: Retrospective evaluation of a single surgeon cohort. All patients over 18 years old, undergoing a surgical treatment for histologically confirmed GBM in the stated period were included. We collected information on demographics, tumour volume, EOR, complications, adjuvant therapies, molecular profile, and OS. We used log rank tests and Cox Proportional Hazards Models to identify factors associated with OS. RESULTS: The patient and tumour characteristics of our cohort were similar to those documented in the literature. The mean age was 56.6 years. 72 patients underwent biopsy and 202 had debulking surgery. Median OS was 11 months. Of those debulked, gross-total resection was achieved in 41 patients (20%); associated median OS was 29 months. Patients receiving partial resection (defined as EOR <80%) had no clear survival benefit over patients undergoing biopsy (median OS 6 vs 5 months) but had a higher rate of post-op neurological deficit (3% vs 12%). Tumour molecular profile appeared to influence survival outcome in a manner comparable to worldwide experience. CONCLUSION: In our experience, partial resection is not a justifiable surgical aim in the typical glioblastoma cohort. The limited benefit that it may confer over biopsy appears to be outweighed by the risk of neurological deficit that affects quality and probably quantity of life. This finding applies to our glioblastoma population in general as well as those specifically with an MGM-unmethylated tumour.

BRAIN SURGICAL TISSUE FOR ADVANCED TUMOUR MODELS IN PRECISION MEDICINE: DEVELOPING THE BRAIN-STAT PATHWAY

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

Prospective consent

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

B. Rapid transfer of fresh surgical tissue samples:

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

C. Standardised annotation across disciplines

The RedCAP database system allows granular control over data-access, and each specialist research team is provided access only to the sub-sections relevant to them. All users must have Good Clinical Practice certification and GDPR training, prior to access of the BRAINSTAT database. RESULTS: Between 25/11/2019-16/03/2020 and 27/07/2020-16/11/2020, 65 patients were consented for BRAINSTAT at the weekly neurosurgical oncology clinic. (Recruitment gaps due to the SARS-COVID 19 pandemic). Pathological diagnosis of surplus tissue collected included: 37 high grade glioma, 3 low grade glioma and 16 brain metastasis including: (6 lung, 6 breast, 2 colorectal, 1 oesophageal, 1 endometrial). Meningioma (5 WHO I; 1 WHO III) 1 patient undergoing anterior temporal lobectomy for hippocampal sclerosis contributed access tissue from the lateral neocortex. 1 patient had

a non- neoplastic, non-diagnostic sample. All patients had matched "germline" blood samples.

Median time from resection to arrival in the laboratory was 10 minutes (range 4-31). Standardised operating protocols to optimise this have been developed.

Glioblastoma and breast-brain metastasis tumourspheres and cerebral organoids are currently being validated. CONCLUSION: Despite the challenges of the pandemic we have established a viable tissue pipeline from neurosurgical operating theatre to our university laboratories. We are developing clinically annotated human brain tumour cell lines, stem cells and 3D organoid models, principally for commonly encountered brain tumours such as glioma and metastasis.

The research sets the foundation for a multitude of downstream applications including:

- Building more complex organoid cultures e.g. by including other cell types such as healthy brain cells and endothelial cells allowing future experiments to more accurately model tumour growth.

- Developing high-throughput, patient-specific drug screens of novel drugs and drug combinations using these 3D tumour models aiming to more effectively treat tumour proliferation and spread. These patient avatars will help inform and test more "stratified" personal medical treatments and will provide opportunities to allow earlier intervention with the aim of improving survival, coupled with a better quality of life.

EFFECTS OF THE TUMOUR MICROENVIRONMENT ON PROTOPORPHYRIN IX ACCUMULATION IN GLIOBLASTOMA

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AIMS: Glioblastoma is the most common primary brain tumour and has a poor prognosis. Standard clinical intervention involves the resection of the tumour volume, chemotherapy and radiotherapy. However, achieving gross-total resection is challenging due to poorly defined boundaries as a result of tumour infiltration. Fluorescence-guided surgery (FGS) utilises an apparently selective accumulation of protoporphyrin IX (PPIX) that occurs in areas of glioblastoma after systemic administration of the metabolite 5-aminolevulinic acid (5-ALA). We have investigated the metabolic basis for the heterogeneity of the PPIX fluorescent signal, and its implications for glioma biology. METHOD: Using glioblastoma cell lines and patient-derived primary cells, we have monitored the uptake of 5-ALA and conversion to the fluorescent molecule PPIX. Stable isotope tracing coupled with GCMS and LCMS was used to analyse intra- and extracellular metabolite levels arising from exogenous 5-ALA administration under both normoxic (21% O2) and hypoxic (1% O2) conditions. RESULTS: Uptake of exogenous 5-ALA from culture media and conversion to PPIX is observed in a time and dose-dependent manner in both normoxia and hypoxia. High levels of PPIX accumulation are associated with reduced cell proliferation despite the majority of the PPIX synthesised not being retained within the tumour cell, but exported into the medium. Under hypoxic conditions, reduced fluorescence is observed as a result of the decrease in oxygen availability likely affecting the oxygen-dependent enzymes. Stable isotope tracing experiments indicate an increase in the glutamine-derived succinate pool in response to exogenous 5-ALA, which is dependent on flux through the heme pathway. CONCLUSION: Our data suggest that different microenvironments within the tumour alter the activity of the heme biosynthetic pathway, resulting in differential fluorescence in glioblastoma. It paves the way by which we could work to alter the glioblastoma microenvironment in order to further improve the use of FGS in guiding surgery across these devastating tumours.

THREE-STAGED STEREOTACTIC RADIOSURGERY FOR BRAIN METASTASES: A SINGLE INSTITUTION EXPERIENCE

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AIMS: Stereotactic radiosurgery (SRS) using the Leksell Gamma Knife system is a commonly used modality for the treatment of brain metastases (BMs). As the size of the target volume (TV) increases, so too does the dose of radiation delivered to surrounding healthy tissue. Large BMs are therefore a contraindication to the use of SRS. Critical organs adjacent to the TV may also be a contraindication to SRS. Staged SRS was proposed as a novel method of delivering three SRS treatments at a reduced radiation dose with a gap of two weeks between each session as a way of shrinking the TV. This allows treatment of TVs otherwise considered untreatable with standard, single-fraction SRS. Little data exists in the literature as to its efficacy. The objective of this study was to evaluate the efficacy of this novel approach and to identify factors which may predict treatment failure. METHOD: A retrospective analysis was undertaken at a single, tertiary Gamma Knife centre. All patients who underwent treatment of their BMs with three-staged Gamma Knife SRS from January 2014 to December 2020 were identified and included. Patient demographics and primary cancer status was ascertained. SRS treatment details for each lesion were collected, including TV, dose and dosimetric data. The percentage reduction in volume of the TVs between the first and second stage, the second and third stage and the first and third stage were calculated. Follow-up data was collected to include follow-up imaging, further intracranial treatments received and survival status. The percentage reduction in volume between each stage was demonstrated on box-and-whisker plots. Statistical significance in reduction in TV between each stage was ascertained by paired samples T-tests. Correlation between initial TV size and percentage reduction post-SRS was determined by a correlation coefficient. Differences were deemed significant with p-values <0.05. RESULTS: 12 patients with 14 staged BMs were identified and included. The median age was 61.5 (range 45-79). Seven had a primary malignancy of breast cancer, five non-small cell lung cancer, one melanoma and one colorectal. Median follow-up was 140.5 days (range 10-821). Median TV was 7.44cc (range 1.14-21.53). All TVs received 10Gy at each stage. The median percentage reduction in size of the TV was 7.41% between 1st-2nd stage (range -16.0-42.49%, p-value 0.06), 19.47% between 2nd-3rd stage (range -5.38-53.53%, p-value <0.01) and 24.25% between 1st-3rd stage (range 10.69-68.67%, p-value <0.01). The correlation coefficient between initial TV size and percentage reduction post-SRS was -0.41 (p-value 0.07). 13/14 lesions showed a partial response on first follow-up scan post-SRS, 1/14 lesions showed a mixed response. One patient died 184 days from completion of treatment but without intracranial progression. Two patients had salvage intracranial surgery, 154 and 536 days from completion of treatment respectively. CONCLUSION: Three-staged Gamma Knife is shown to be effective at shrinking the TV and can therefore be used to treat lesions otherwise considered unsuitable for SRS. The presence of extra-cranial metastases did not predict for poor outcomes. Though local control with SRS is thought to diminish with increasing TV size, all staged lesions showed a reduction in size between first and last treatment, and no significant effect was seen between initial TV size and percentage reduction in TV. No patients experienced disease progression on first follow up scan, with 13 of 14 lesions showing disease response. There were only two cases of intracranial progression, with one occurring 536 days post-SRS. Though limited by small numbers and short median follow up period, our data demonstrate encouraging results for three-stage SRS for lesions otherwise unsuitable for single fraction treatment, and should lead to further study.