Glioblastoma in the older population: clinical, pathological and imaging approaches to personalising treatment

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Abstract

Background: Glioblastoma (GBM) is the commonest primary malignant brain tumour in adults. Incidence increases with age and prognosis is poor. Clinical trials have established modest survival benefits in older patients from single and combined chemo-radiotherapy treatment regimes however those recruited into the clinical trials do not well represent this heterogeneous population. A comprehensive evaluation of the clinical and radiological basis by which treatment decisions are made is lacking in the UK population.

Aims: To explore pre-treatment characteristics in older GBM patients that could predict for overall survival. To test the feasibility of implementing a geriatric assessment (GA) for older GBM patients. To investigate pre-treatment imaging parameters that predict radiation induced toxicity in older patients with GBM.

Methods: The chapters of this thesis cover: (1) a comprehensive literature review, (2) a multicentre retrospective cohort study, (3) a population based cross-sectional survey of neuro oncology consultants in the UK, (4) a multicentre prospective feasibility trial implementing a GA within outpatient neuro-oncology clinics; and (5) a prospective pilot study exploring the predictive value of MRI imaging parameters in this population, leading to a multicentre, prospective cohort imaging study.

Results: There is a paucity of evidence surrounding the use of GA tools within the neuro oncology population and most currently practicing UK neuro oncology consultants do not routinely use any cognitive or geriatric assessment tools. Pre-treatment clinical and radiological features exist which independently predict for overall survival. The use of a neurologically focussed GA tool was feasible and acceptable to both staff and patients within busy NHS outpatient clinics and the results of this GA were associated with overall survival. Pilot data suggests that Global Cortical Atrophy and Medial Temporal Lobe atrophy scores from pre-treatment MRI scans can predict the likelihood of experiencing CTCAE Grade 3 or 4 acute side effects from cranial radiotherapy.

Conclusion: Older patients with GBM represent a vulnerable and under-researched cohort. A neurologically focussed GA could be used to help predict

which patients are more likely to benefit from active treatment, enabling clinicians to have more informed and individualised treatment discussions with patients. Further work is needed to validate which sections of the neurologically focussed GA are predictive amongst a larger group and whether GBM patient specific interventions can be implemented to improve outcomes. Imaging biomarkers from pre-treatment MRI scans may help predict which patients are more likely to suffer from radiotherapy induced side effects.

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Glossary

5-ALA	5-Aminolevulinic Acid
ANOCEF	Association des Neuro-Oncologue d'Expression Française
ASCO	American Society of Clinical Oncology
BSC	Best Supportive Care
CCI	Charlson Comorbidity Index
CGA	Comprehensive Geriatric Assessment
CNS	Clinical Nurse Specialist
CRT	Chemo-Radiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
G8	Geriatric 8
GBM	Glioblastoma
GCA	Global Cortical Atrophy
G-CIMP	Glioma CpG island methylator phenotype
GTR	Gross Total Resection
H3F3A	H3 Histone Family Member 3A
HADS	Hospital Anxiety and Depression Scale
HR	Hazard Ratio
IADLS	Instrumental Activities of Daily Living
IDH	Isocitrate dehydrogenase
KPS	Karnofsky Performance Status
MARS	Microbleed Anatomical Rating Scale
MDM	Multidisciplinary Meeting
MGMT	O-6-Methylguanine-DNA Methyltransferase
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MTA	Medial Temporal Lobe Atrophy
NHS	National Health Service
OR	Odds Ratio
PPI	Proton Pump Inhibitor
PRDX1	Peroxiredoxin 1
PTEN	Phosphatase and tensin homolog
QLQ	Quality of life Questionnaire
RT	Radiotherapy
SIOG	International Society of Geriatric Oncology
STR	Subtotal resection
TERT	Telomerase reverse transcriptase
TMTB	Trail Making Test B
TMZ	Temozolomide
VES-13	Vulnerable Elders Survey – 13
WHO	World Health Organisation

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Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree, and does not incorporate any material already submitted for a degree.

Signed: 

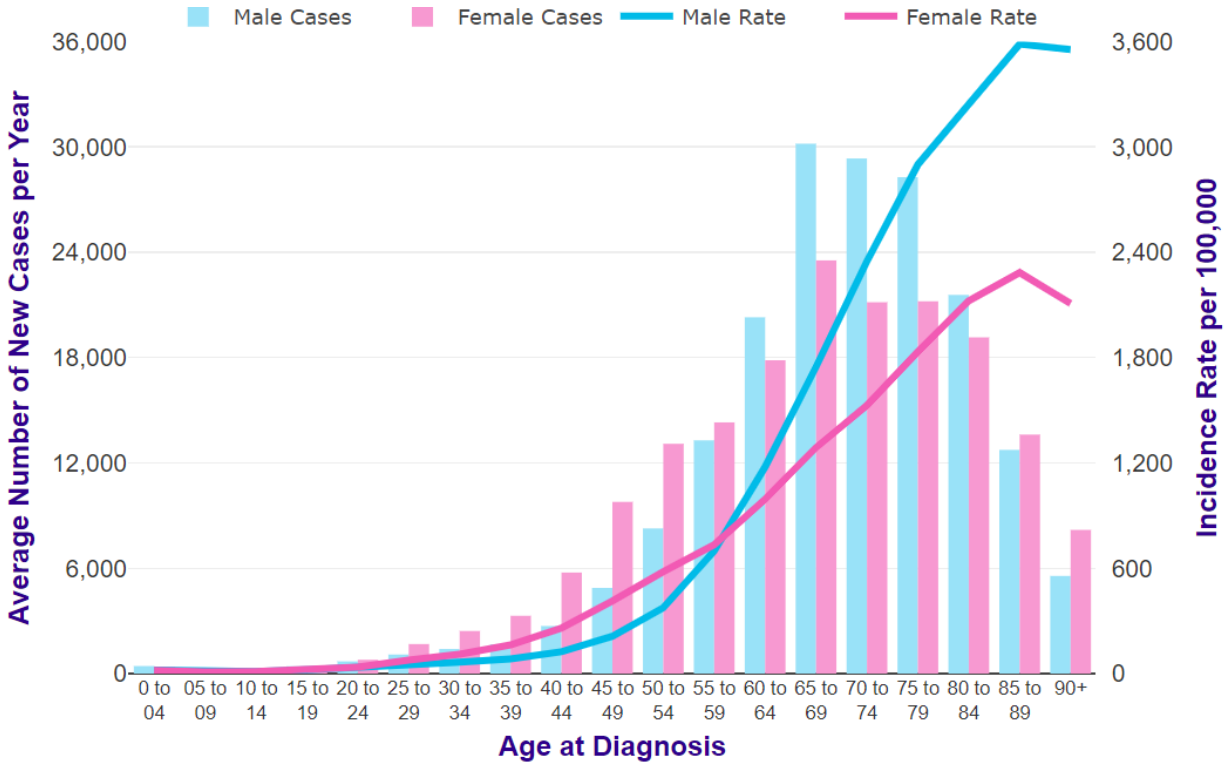
Name: Cressida Flora Kate Lorimer

Dated: 28.5.19

Chapter 1 Introduction and review of the literature

The global population is ageing with the United Nations predicting that the number of people aged 60 or over will more than double by 2050 and to more than triple by 2100. Globally, the population aged 60 or over is growing faster than all younger age groups[1]. In the UK between 1981 and 2012 life expectancy rose by 6 years for women and 8.2 years for men[2]. National life expectancy is predicted to reach at least 84.5 years for women and 81.4 years for men by 2030. This is of increasing relevance to oncologists as, across almost all adult tumour types within oncology, approximately 60% of the cancer incidence and 70% of cancer mortality occurs among adults age 65 and older[3,4], see Figure 1[5]. Within oncological research this global ageing pattern has been reflected in an increase in focus on how we approach older cancer patients. The definition of who represents an 'older' cancer patient is difficult, with age cuts offs ranging from 60 to 85. The World Health Organisation neatly summarised that there is no 'typical' older person and therefore research and strategy should be aimed to address the needs of all older patients[6].

Figure 1 Cancer Research UK figures for cancer incidence by age (original in colour)



Glioblastoma (GBM) is the commonest primary malignant brain tumour, with incidence rates of 4.6/100,000/year in the UK. The mean age of diagnosis is 64 and incidence rates peak in 65-75 year olds[7]. Improved life expectancy worldwide has led to a doubling of incidence rates of GBM in the over 65s from the 1970s to 1990s[8]. Older patients with GBM do worse than their younger counterparts, with average life expectancy in the range of 3-6 months compared to 12-18 months[7]. The causes for this are poorly understood, however more aggressive tumour biology, under treatment and decreased biological reserve play a part in this patient group. The age at which a person becomes 'older' with GBM has shifted over the years with recursive partitioning analysis showing a difference in outcomes appearing as early as 40 years[9]. As the global population ages, the rates of GBM are predicted to rise further. There is an urgent need to improve outcomes amongst this vulnerable and under researched cohort.

Until recently there has been a paucity of data surrounding the treatment of older people with cancer. Trials often have an upper age limit in their inclusion criteria and trials specifically aimed at older patients are rare[10,11]. The American Society of Clinical Oncologists has sought to redress this balance with a 2015 publication highlighting the importance of developing research knowledge across tumour types in the elderly cohort[12]. ASCO have followed this up with a set of guidelines in 2018 for older people receiving chemotherapy[13] and Cancer Research UK and The International Society of Geriatric Oncology have followed suit[14,15].

Within neuro-oncology the optimal treatment regime for older GBM patients is still unstandardized and age alone has been most often used as a cut off for inclusion within clinical trials. There is a growing momentum behind the use of more comprehensive assessment tools to assess biological rather than chronological age and help predict which patients may benefit from treatment. However the basis on which clinical decisions are made is as yet unstandardised and the work in other tumour sites on improved assessment techniques of older people with cancer has yet to break through into neuro

oncology. We therefore do not yet have a firm evidence base on which to base clinical treatment decisions amongst the older GBM population.

1.1 Thesis aims

The older population of patients with GBM are an inherently complex group, given the natural symptom burden of ageing in combination with the physical and psychological effects of an aggressive brain tumour. There are a number of treatment options available within this group however there is a need to improve the clinical premise by which treatment decisions are made, given that no intervention is without side effects. The older GBM cohort is a vulnerable and often overlooked patient group where treatment decisions need to be carefully balanced by quality of life and toxicity risks. There is a paucity of robust clinical trial evidence, both within elderly oncology patients as a whole and particularly within the rare sub group of neuro oncology.

This thesis aims to explore the diagnostic and treatment pathway for older GBM patients, and incorporate work done within other tumour sites using geriatric assessment tools into the neuro oncology patient group.

1.1.1 Aims

- To undertake a literature review of the evidence base of treatment for older GBM patients and the use of geriatric assessments within the oncological setting, focussing on neuro oncology patients.
- To explore, via a retrospective series, whether there are pre-treatment clinical, pathological and imaging factors that can effect patient outcomes independent of treatment received in order to help design a clinical assessment tool focussed on the particular characteristics of this population.
- To analyse, by means of a cross sectional survey, the current working practices in neuro oncology patient clinics in the UK. To explore current use of assessment tools to decide on fitness for treatment and the availability of multidisciplinary support.
- To test the feasibility of incorporating a neuro-oncologically focussed geriatric assessment tool with newly diagnosed older GBM patients

within the confines of an NHS clinic. To the author's knowledge, this is the first such study performed within the older neuro oncology community.

- To focus on the use of radiological markers to help predict which patients may be more or less likely to experience acute side effects from cranial radiotherapy in order to help guide treatment decisions within this cohort.

1.2 Review of the literature

This literature review examines the potential factors contributing to the poorer prognosis of the elderly cohort including biological and imaging factors, the current treatment strategies in the elderly GBM population and the evidence published to date on the use of geriatric assessment tools within geriatric oncology as a whole and particularly with the neuro oncology cohort.

A search was performed on MEDLINE and EMBASE using the terms *glioblastoma AND *elderly OR *geriatric OR *elderly assessment OR *cognitive. This resulted in 5211 references after filtering for age over 65 years and English language only. These were reviewed and case reports, abstracts and those not translated into English removed.

1.2.1 Biology of GBM in older patients

The majority of glioblastomas in older patients arise de novo, evolving rapidly with a short history of clinical symptoms, so called 'primary' GBMs. Younger patients tend to develop glioblastomas from the transformation of lower grade astrocytomas over a longer time period, so called 'secondary' GBMs. Histologically the two types of glioblastomas seem identical, however differences become apparent with genetic and epigenetic analysis[16]. Glioblastomas which evolve from lower grade gliomas tend to contain a mutation in the isocitrate dehydrogenase 1 gene (IDH1) which de novo glioblastomas lack and this has been shown to be of greater prognostic significance than histological diagnosis[17]. In 2016 the WHO reflected this by publishing a new classification of CNS tumours, integrating phenotypic and genotypic features into their system. This now contains 3 types of GBM; GBM IDH-wildtype, GBM IDH-mutant and GBM NOS, replacing the previous 'primary'

and ‘secondary’ classifications[18]. Genetic sequencing of GBM samples by The Cancer Genome Atlas Research Network revealed 4 distinct subtypes of GBM; proneural, neural, classical and mesenchymal. The proneural subtype has characteristics traditionally associated with secondary GBMs however a number of the samples that were examined had come from clinically diagnosed primary GBMs and it may be that these share a common developmental pathway with secondary GBMs or reflect clinically silent lower grade tumours that transformed prior to diagnosis. The proneural subtype was significantly associated with a younger age at presentation and conferred a better prognosis[19].

O(6)-methylguanine-DNA methyltransferase (MGMT) gene codes for the MGMT protein which repairs DNA lesion O(6)-methylguanine back to guanine and prevents mismatch errors during DNA replication. It has been shown to be crucial in the response of GBMs to alkylating chemotherapy. In tumours where there is epigenetic silencing of the MGMT promoter region, a significant and durable increase in sensitivity to alkylating chemotherapy, such as temozolomide, has been shown[20]. MGMT has become a prognostic and predictive biomarker in the treatment of GBMs with around 45-50% of GBMS exhibiting methylation of promoter region[21]. Unlike IDH1 mutations, the prevalence of MGMT methylation appears unaffected by age[22].

Further work has been performed by Batchelor et al who examined 140 consecutive glioma specimens in patients ranging from 16 to 84 years (median age 60 years) for allelic loss of 10q, EGFR amplification, CDKN2A/p16 deletion, loss of 19q, TP53 mutations and loss of 1p. In patients aged over 70 years, TP53 alterations and CDKN2A/p16 deletion were associated with reduced survival whereas the opposite was true in younger counterparts. In patients under 46 years, EGFR amplification was associated with reduced survival whereas the opposite was true in patients over 46 years. The good prognostic effect of LOH 1p was more pronounced in patients over 60 years than those under 60 years. In multivariate models only TP53 and EGFR remained significant[23].

The NOA-08 collective were the first to compare the prevalence of survival associated molecular biomarkers in an elderly cohort of patients to younger control groups where these biomarkers have been validated. Favourable prognostic biomarkers such as IDH or H3F3A mutation, G-CIMP, or PRDX1 methylation were found to be virtually absent in the tumours of the older patient cohort they tested. The study group concluded that, as they had a small number of patients with an unusually greater than average overall survival who did not test positive for any of the favourable known biomarkers, there is still work to be done to explore unknown prognostic biomarkers specific to the elderly population[24].

1.2.2 Treatment strategies to improve survival for older patients with GBM

Surgery

The clinical significance of the extent of surgery performed on GBM patients was debated for decades however a recent systematic review and meta-analysis alongside numerous retrospective studies has concluded that amongst those involved in clinical trials, gross total resection confers improved survival compared to sub-total resection or biopsy[25,26]. Thus for patients aged under 65 years, standard of care is for gross total resection when possible. As is the case in much of oncology research, the data is lacking in older patients as, in the majority of the clinical trials involved in the systematic review, patients over the age of 65 were excluded.

There is concern, given the poor prognosis within the older cohort, that aggressive treatment may involve toxicities which outweigh the conservative survival benefits. Older patients tend to be frailer and more likely to suffer co-morbidities which may make them more susceptible to the side effects of treatment. This is relevant in terms of the extent of surgical resection performed and it has been shown that older GBM patients are less likely to undergo macroscopic resection than their younger counterparts[27]. In general, as patients age they become more sensitive to the side effects of anaesthetic agents. This is in part due to an increased likelihood of comorbidities and interactions from polypharmacy and also because elderly patients are known to have poorer

temperature regulation and less effective immune systems than their younger counterparts[28]. With effective anaesthetic management it is difficult to tell whether these factors would have a significant effect on patient outcome. Trials looking at anaesthetic risk in older GBM patients are sparse; a small retrospective study performed on 88 patients aged between 31 and 78 found age had a significant effect on the likelihood of experiencing a post-operative complication but pre-operative anaesthetic status did not[29]. Despite this, a number of retrospective reviews have shown that the positive benefit of maximal surgical resection seen in younger patients continues into the older cohort if patients are selected correctly[30-35]. Only 1 prospective study has been published which randomised patients to stereotactic biopsy or open craniotomy and resection. Although this was conducted in a small population, a modest improved overall survival of 175 days was seen in the craniotomy arm compared to 85 days in the biopsy arm ($p=0.035$)[36].

A trial by Stummer *et al* showed that tumour fluorescence derived from 5-aminolevulinic acid (5-ALA) enables more complete resection of contrast-enhancing tumour (65% vs 36% achieved gross tumour resection). This led to a higher 6-month progression free survival (41.0% vs 21.1%) but only a small number of elderly patients were included[37]. There is little data to guide the use of 5-ALA in older GBM patients.

The evidence supporting gross total resection in elderly patients is based mainly on retrospective reviews and therefore is subject to bias. It is likely that those who had a good performance status, fewer comorbidities and potentially less significant neurological deficit were therefore fit enough for surgery and likely to undergo resection rather than biopsy, however the increasing number of retrospective reviews showing a positive prognostic effect of resection suggest that, with proper pre-operative optimization, age should not a be a barrier to craniotomy and resection.

Standard oncological care for patients under 65 years

Treatment for patients aged 70 years or under with GBM was established in 2005 when the EORTC-NCIC trial compared radiotherapy alone (60Gy in 30#)

to radiotherapy with the addition of the oral alkylating agent temozolomide (TMZ) in the concomitant (daily 75mg/m^2) and adjuvant (daily 150-200mg/m^2 for 5 days of each 28 day cycle for 6 months) setting. The trial was performed in patients who had received maximal safe surgical resection, with WHO performance status 0-2 and aged between 18 and 70. Median survival was 12.1 months in the radiotherapy alone arm compared to 14.6 months in the radiotherapy plus TMZ arm, establishing the addition of TMZ to radiotherapy treatment as standard of care for patients within the trial eligibility criteria [38]. Subsequent analysis however revealed the overall survival benefit failed to reach significance in the 65-70 year old age group (HR = 0.78 [0.50–1.24], p = 0.29) and treatment regimens for those over 65 are therefore less straightforward[39].

Oncologists have extrapolated the data from the EORTC trial and used the Stupp regime in fitter older patients with good results. All of those published have been retrospective studies, often single centre with the patients subject to inevitable selection bias, however improvements in survival to those seen in the EORTC patient cohort are reported[40-42].

There is concern that the side effect profile associated with the Stupp regime from the EORTC trial may be too toxic for those patients who are older or less fit and there is debate over the degree of survival benefit gained by treatment amongst this patient cohort. There is ongoing debate about the best treatment regimes to be used in those over 65 years and a number of randomized clinical trials have been published over the last few years which have looked at alternative radiotherapy and chemotherapy regimens designed to lessen the treatment intensity and side effect burden whilst maintaining a survival benefit.

Radiotherapy treatment

Radiotherapy has been a mainstay of treatment for brain tumours since the 1940s, initially with whole brain radiotherapy using kilovoltage x-rays but gradually becoming more sophisticated with the use of ^{60}Cobalt machines or megavoltage x-rays. Work done by The Brain Tumour Study Group in the 1970s conclusively demonstrated that post-operative radiotherapy conferred improved

survival compared to best supportive care or chemotherapy alone[43,44]. Around this time improved imaging techniques allowed some groups to develop 2 phase radiotherapy regimens involving a lower dose to the whole brain with a boost to the tumour. This was associated with improved survival and developed further by Walker et al from The Brain Tumour Study Group who explored dose escalation and set the standard of 60Gy which is used to this day. They showed that doses of 60Gy were associated with 2.3 times the median survival compared to no radiotherapy and 1.3 times the median survival of doses less than or equal to 45Gy[45].

In 2003 Brada showed a shorter palliative regime of 30Gy in 6 fractions maintained or improved patients' functional status in an older and poorer prognosis group. Median survival was 5 months with a 1 year survival of 12% and although the survival benefit was 2.5-4.5 months higher in age matched patients from MRC controls treated with 60Gy in 30 fractions, the hypofractionated regime was well tolerated with fewer side effects than radical treatment [46]. The 2007 ANOCEF trial examined the effect of a higher dose of radiotherapy compared to best supportive care on overall survival and quality of life in older GBM patients. Median and progression free survival improved from 16.9 to 29.1 and 5.4 to 14.9 weeks respectively in patients treated with 50Gy in 1.8Gy daily fractions[47]. This trial was done in a small group of patients with an initial KPS of $\geq$ 70 and showed no significant difference in EORTC QLQ scores between groups. However, the small increase in median survival must be balanced by the daily trips to hospital required by 6 weeks of treatment.

Older GBM patients are more likely than their younger counterparts to receive shorter hypofractionated regimes of radiotherapy if used without chemotherapy. The use of these regimes has increased recently from 7% in 2005 to 19% in 2012 [48]. However, a retrospective study using the National Cancer Database in America showed that if given as part of an adjuvant regime with chemotherapy, most patients seem to receive a radical dose of 60Gy in 30#. There was no difference in 30 day mortality between those receiving standard or hypofractionated radiotherapy however 60 and 90 day mortality were 13.5% and 24.3% in the standard group and 19.6% and 32% in the hypofractionated

group respectively ($p<0.01$). The authors put forward the argument that hypofractionated regimes can improve the survival to treatment time ratio and therefore potentially have a positive effect on quality of life[49].

Although overall survival is traditionally used as the primary end point in studies, there has been increasing interest in quality of life (QoL) measures, especially relevant given the poor prognosis of this patient cohort. In 2004 Roa et al demonstrated equivalent survival outcomes between 40Gy in 15 fractions and the conventional 60Gy in 30 fractions (5.6 months vs 5.1 months respectively, log rank test $p=0.57$) in GBM patients aged 60 or over. The trial team attempted to measure QoL however had poor return on the FACT-Br questionnaires and so could not draw conclusive results. However, Karnofsky Performance Status (KPS) did not vary significantly between the two groups of patients over the course of treatment and only 23% of patients in the hypofractionated arm required an increase in their corticosteroids compared to 49% in the standard treatment arm ($p=0.02$). The trial team concluded that 40Gy in 15# was an acceptable treatment regime amongst older GBM patients[50].

Roa took this work further with The International Atomic Energy Agency trial in 2010, comparing 40Gy in 15 fractions to an even shorter regime of 25Gy in 5 daily fractions. The trial recruited frail and/or elderly GBM patients, defined as frail = age ≥ 50 years and KPS of 50% to 70%; elderly and frail = age ≥ 65 years and KPS of 50% to 70%; elderly = age ≥ 65 years and KPS of 80% to 100%. They showed non inferiority in survival between the two arms with median survival of 7.9 months in the 25Gy in 5 fraction arm and 6.4 months in the 40Gy in 15 fraction arm. More interestingly, there was no difference in quality of life at 4 and 8 weeks post treatment as measured by the EORTC QLQ-C30 and QLQ-BN20 questionnaires [51].

Hypofractionated radiotherapy regimes have thus become viable treatment options in those patients who are not fit for conventional radical chemotherapy. However there is growing interest in abbreviating the Stupp regime of chemoradiotherapy or using chemotherapy alone in patients felt not to be robust enough to tolerate the radical regime.

Chemotherapy and chemoradiotherapy

One way of stratifying patients for treatment has been the use of prognostic and predictive biomarkers. Within GBM, O6-methylguanine DNA methyltransferase (MGMT) promoter methylation and IDH1/2 mutation status are the two biomarkers used in routine practice. IDH 1/2 mutations are associated with secondary GBMs which tend to confer better prognosis, regardless of treatment received[16,52]. The incidence of secondary GBMS (and therefore IDH 1/2 mutations) decreases with age[17]. MGMT promoter methylation rates are independent of patient age. The prognostic effect of MGMT promoter methylation was validated within the EORTC Stupp trial[53] and has been subsequently confirmed within the elderly population[22]. Due to the shorter life expectancy and potential for greater side effects within the older population, interest has gathered around omitting radiotherapy and treating with chemotherapy alone.

In 2004, Chinot at el established TMZ as a safe and relatively well tolerated single agent treatment in an open label Phase II trial involving patients aged over 70 with a radiologically or histopathologically newly diagnosed GBM. They treated 32 GBM patients aged 70 or over with daily TMZ 150mg-200mg/m^2 for 5 days of a 28 day cycle until progression. Median survival was 6.4 months with mild adverse reactions, NCI CTC Grade 3-4 thrombocytopenia and neutropenia reported to occur in 6% and 9% of patients, respectively. Quality of life was not measured in this study but data on performance status, steroid use and a mini mental state exam were collected during the TMZ therapy. The authors conclude that 50% of patients improved on TMZ as their KPS improved by 1 point or the MMSE score improved by 5 and these were associated with a stable or decreased steroid dose[54].

The publication of two large randomized controlled Phase III trials in 2012, NOA-08 and the NORDIC study, examined the role of single agent TMZ with interest in the potential of MGMT promoter methylation as a predictive biomarker. The German NOA-08 study randomised patients aged over 65 with a KPS of 60 or more and high grade glioma to receive dose-dense TMZ (100 mg/m^2 temozolomide, given on days 1-7 of 1 week on, 1 week off cycles) or

radical radiotherapy alone with 60Gy in 30 fractions. TMZ was not inferior to RT with median overall survival of 8·6 months (95% CI 7·3-10·2) in the TMZ group versus 9·6 months (8·2-10·8) in the radiotherapy group (hazard ratio [HR] 1·09, 95% CI 0·84-1·42, p(non-inferiority)=0·033). MGMT promoter methylation data was available in 35% of the patients recruited. Patients with MGMT promoter methylation showed longer overall survival than those unmethylated (11.9 vs 8.2 months; HR 0·62, 95% CI 0.42-0.91, p=0.014). Event free survival was longer in patients with MGMT promoter methylation who received TMZ than in those who underwent radiotherapy (8·4 vs 4·6 months), whereas the opposite was true for patients with an unmethylated MGMT promoter (3·3 vs 4·6 months). Quality of life as measured by EORTC QLQ-C30 and QLQ_BN20 revealed significant problems with communication deficits in the radiotherapy arm [55].

The NORDIC study randomized patients aged over 60 (changed to over 65 after the publication of the Stupp trial during their recruitment period) with a new histopathological diagnosis of GBM with WHO performance status of 0-2 to TMZ (200mg/m^2 for 5 days every 28 day cycle for 6 cycles), radical RT (60Gy in 30 fractions over 6 weeks) or hypofractionated RT (34Gy in 10 fractions at 3.4Gy per fraction over 2 weeks). In the over 70 cohort, TMZ and short-course RT were equivalent and superior to radical RT; HR for temozolomide vs standard radiotherapy 0·35 [0·21-0·56], p<0·0001; HR for hypofractionated vs standard radiotherapy 0·59 [95% CI 0·37-0·93], p=0·02). Again MGMT was shown to have prognostic and predictive effect as a biomarker with those who had tumour MGMT promoter methylation showing significantly longer survival than those without MGMT promoter methylation (9·7 months [95% CI 8·0-11·4] vs 6·8 months [5·9-7·7]; HR 0·56 [95% CI 0·34-0·93], p=0·02) if the TMZ arm. No difference was noted between those with methylated and unmethylated MGMT promoter treated with radiotherapy (HR 0·97 [95% CI 0·69-1·38]; p=0·81) [39]. The quality of life data from this trial has to be interpreted with caution given the low number of EORTC QLQ-C30 and QLQ-BN20 questionnaires returned at 3 months however they suggest a better quality of

life within the TMZ alone group although equal ratings for global health across the three groups.

The use of single agent TMZ is now supported in elderly patients with MGMT promoter methylation however there has been increasing interest in the use of concurrent TMZ and radiotherapy in more tolerable schedules for older patients. Expanding on the use of hypofractionated radiotherapy regimes, the CCTG CE.6/EORTC 26062 Canadian study published by Perry et al in 2017 randomised patients to 40.05Gy in 15 daily fractions of radiotherapy over 3 weeks with or without the addition of temozolomide concomitantly (75mg/m^2 daily for 21 consecutive days) and adjuvantly (150-200mg/m^2 daily for 5 days every 28 day cycle for up to 12 cycles or progression). Patients were aged 65 or over, ECOG performance status 0-2 and deemed by their treating physician to be unsuitable for radical treatment with 60Gy in 30# with concurrent and adjuvant TMZ. Median overall survival was longer with the addition of TMZ (9.3 months vs. 7.6 months; hazard ratio for death, 0.67; 95% confidence interval 0.56 to 0.80; P<0.001). 63% of patients had MGMT results available; 29% of patients had promoter methylation. In line with other studies, MGMT methylation status was significant in predicting response to chemotherapy with median overall survival of 13.5 months with radiotherapy plus temozolomide and 7.7 months with radiotherapy alone (hazard ratio for death, 0.53; 95% CI, 0.38 to 0.73; P<0.001) in the methylated group. Of those who were unmethylated, the median overall survival was 10.0 months with radiotherapy plus temozolomide and 7.9 months with radiotherapy alone (hazard ratio for death, 0.75; 95% CI, 0.56 to 1.01; P=0.055; P=0.08 for interaction). Quality of life was measured using EORTC QLQ-C30 and QLQ-BN20 and showed no significant difference between the two groups[56].

There is now evidence to support the use of chemotherapy or radiotherapy concurrently or alone amongst the elderly GBM population. The skill in geriatric oncology is determining clinically which patients are likely to be able to withstand the side effects of treatment in order to gain the benefits. The use of the biomarker MGMT can help guide chemotherapy decisions however the

clinical basis on which treatment strategies are determined remains heterogeneous and under researched.

1.2.3 Imaging in older GBM patients

Radiotherapy is the mainstay of treatment for GBMs of all ages. Toxicities from radiotherapy can be divided into acute, subacute and late effect. In the first few weeks these are thought to be due to radiation-induced cytokine release and vasodilation resulting in increased edema and disruption of the blood–brain barrier. Clinically this can manifest as fatigue, nausea, confusion, seizures and a need for increased steroid doses. Sub-acute effects include somnolence syndrome where patients can feel clumsier and sleep for up to 20 hours a day[57]. A number of theories have been proposed for the cause of this, the predominant one being temporary disruption of the myelin sheath covering of the axons[58]. Long term side effects typically occur from 6 months after the end of treatment and are thought to be irreversible due to permanent radiation induced damage to the white matter. These can include decreased intellect, memory impairment, confusion, personality changes, and alteration of the normal function of the area irradiated.

Predicting the degree of side effects an individual patient is likely to experience is difficult. Classically the degree of toxicity is thought to be secondary to radiation dose, fractionation and field size however recent developments in imaging and radiotherapy delivery techniques have improved the side effect profile. A retrospective review of GBM patients in 14 RTOG trials who underwent cranial irradiation with a median dose of 60Gy revealed that older age, poor performance status, aggressive surgery, pre-existing neurological dysfunction, poor mental status and twice-daily radiation were associated with increased acute toxicities[59].

Within the older GBM population, there is greater interest in acute and subacute toxicities due to the poorer life expectancies within this population making late effects less relevant. Many of the acute side effects of cranial irradiation can mimic or worsen common geriatric conditions such as gait disturbance, confusion and fatigue. MGMT promoter methylation status has been used as a

prognostic and predictive biomarker within the older GBM population to guide chemotherapy treatment decisions. As yet there is no such biomarker available for radiotherapy.

MRI imaging has been used to assess the effects of radiation induced neuro toxicity[60] but has not yet been tested in the pre-treatment domain to help predict who may be more sensitive to the toxicities of radiation. There are a number of theories surrounding the pathophysiology of radiation induced brain injury, the predominant of which is the vascular hypothesis[61]. Acute side effects in particular are thought to be due to damage to the cerebrovascular system. The use of MRI to assess background microvascular damage to the cerebral cortex has been developed predominantly in dementia studies[62] and shown to correlate with disease severity. Given the damaging effect of radiation on cerebrovasculature, it is likely that older GBM patients with higher background levels of microvascular damage may be more susceptible to side effects from treatment. This has been explored in a small pilot study which suggested a correlation between higher scores of white matter disease on pre-treatment MRI and survival in GBM patients but as yet this has not been developed further[63].

1.2.4 Assessment of older patients with cancer

There are a number of difficulties in treating the elderly population with cancer; the lack of good clinical trial evidence, complications of multiple comorbidities and polypharmacy, social concerns with mobility and carer responsibilities and therapeutic nihilism to name a few. It is well known that older patients are underrepresented in clinical trials, the US Food and Drug Association reviewed the age related enrollment of new patients into clinical trials and found that from 1995 to 2002 the proportions of the overall patient populations enrolled into trials aged > or = 65, > or = 70, and > or = 75 years were 36%, 20%, and 9% compared with 60%, 46%, and 31%, respectively, in the US cancer population[64]. The low proportion of elderly patients with cancer admitted into clinical trials reflects the paradoxical situation that therapeutic treatments are generally not tested in the population where they are most relevant and have the highest incidence. The European Organisation for Research and Treatment of Cancer (EORTC) tried to address this in 2010 with the publication of a

position paper suggesting ways to incorporate more elderly patients into trials[65], and the American Society of Clinical Oncology (ASCO) followed on in 2015 with 5 recommendations to address the concern over the lack of representation. These include (1) Use clinical trials to improve the evidence base for treating older adults with cancer, (2) leverage research designs and infrastructure for generating evidence on older adults with cancer, (3) increase US Food and Drug Administration authority to incentivise and require research involving older adults with cancer, (4) increase clinicians' recruitment of older adults with cancer to clinical trials, and (5) use journal policies to improve researchers' reporting on the age distribution and health risk profiles of research participants[12].

Assessment of older patients with brain tumours is arguably more challenging than for other tumour groups due to the subtle deficits produced by tumour location and pressure effects. Isolating these from pre-existing comorbidities, and predicting which will have a greater impact on quantity and quality of life is complex, making it difficult to predict which patients will benefit from active treatment.

1.2.5 Comprehensive geriatric assessment

It is well documented that chronological age often correlates poorly with biological age and is insufficient to predict for fitness or frailty[66]. There is therefore interest in other techniques, both biological and clinical, in order to accurately estimate a patient's 'true' age. Many clinical trials use performance status as a marker for fitness however this has a poor correlation with frailty when looking at the elderly population[67,68]. A more comprehensive appraisal is provided by a geriatric assessment, compromising of multiple domains with a holistic approach to producing a review of the patient as a heterogeneous entity. In 2005 the International Society of Geriatric Oncologists (SIOG) gathered a panel of experts in order to assess the evidence behind using a comprehensive geriatric assessment (CGA) in older cancer patients. They conducted a systematic review and concluded that a CGA both highlights problems that are missed by a routine clinical assessment and can improve the function and reduce hospitalisation of elderly cancer patients[69]. Within the oncological

population, studies have shown CGA to predict for survival, post-operative morbidity and mortality and chemotherapy associated toxicities[67,70].

The National Comprehensive Cancer Network, the European Organisation for Research and Treatment of Cancer and the International Society for Geriatric Oncology now recommend that all oncology patients aged 70 and over undergo a geriatric assessment[65,69,71]. In 2018 the American Society for Clinical Oncology published guidelines for assessing and managing older patients receiving chemotherapy and recommended again that all patients over the age of 65 should receive a geriatric assessment in order to *'identify vulnerabilities that are not routinely captured in oncology assessments'*[13].

Despite the number of recommendations published by international oncology groups, there is a difficulty in determining exactly what comprehensive geriatric assessment (CGA) involves. It classically covers domains including functional status, medical (including polypharmacy, comorbidities and nutritional status), cognition, mental health status, social status and support, fatigue and environment[72]. The tools that can be used to assess these domains are numerous (see Table 1.1). Although in the literature the terms are often interchanged, a comprehensive geriatric assessment differs from a geriatric assessment in that it also involves performing goal directed interventions, when deficits are found, in order to correct them[73]. This involves a much larger team than a physician alone and is best managed with a multi-disciplinary group including physiotherapists, occupational therapists, dieticians, social workers and often a geriatrician. These assessments were originally designed for the general geriatric population rather than within the oncological cohort. These services are not easily accessible with the resources and time pressures experienced by the average oncology outpatient clinic. There has therefore been a move towards developing shorter screening tools to highlight patients that are more at risk and should be referred for a fuller assessment. A number of these tools exist within geriatric oncology and as yet there is no international consensus as to the most appropriate within the older oncological population.

Table 1-1 Geriatric Assessment domains and potential screening tools

Domain	Tool
Level of function	Activities of Daily Living (ADL)
	Instrumental Activities of Daily Living (IADL)
	Barthel Index of Activities of Daily Living
Falls	Timed Up and Go (TUG)
	Single question
Memory	Abbreviated Mental Test (AMT)
	Mini Mental State Examination (MMSE)
	Montreal Cognitive Assessment (MoCA)
Nutrition	Mini Nutritional Assessment (MNA)
	Malnutrition Universal Screening Tool (MUST)
	Body Mass Index (BMI)
Co morbidities	Charlson Comorbidity Index (CCI)
	Adult Comorbidity Evaluation 27 (ACE-27)
Mood	Hospital Anxiety and Depression Score (HADS)
	Geriatric Depression Scale (GDS)
	Patient Health Questionnaire 9 (PHQ9)
Polypharmacy	Screening tool for older people's potentially inappropriate prescriptions:Screening tool to alert doctors to right/appropriate treatments (STOPP/START)
	Medication Appropriateness Index (MAI)

1.2.6 Geriatric assessment screening tools

The EORTC tried to address the disparity in geriatric assessment tools used in 2010 by publishing an 'Elderly Minimal Dataset'. This included four elements or assessment tools which they recommended form the backbone of future assessment in clinical trials involving elderly patients in order to provide cross-study comparison. These are the G8 questionnaire, Independent Activities of Daily Living questionnaire (IADLS), Charlson Comorbidity Index (CCI) and data about social situation [74].

In 2015 SIOG updated its guidelines and reviewed the screening tools used within the oncological setting. In the seven years between their publications there had been a significant amount of work published and they reviewed 17 different tools in all. Their consensus statement reports that a screening tool should not replace a geriatric assessment however given the pressures of an outpatient setting, one can be used to identify those patients who may benefit from a more detailed assessment[75]. They concluded that, although the clinical setting may determine which screening tool is most appropriate at the time, the G8 screening tool appeared the most robust.

ASCO recommends that at a minimum, a geriatric assessment should cover an assessment of function, comorbidity, falls, depression, cognition, and nutrition. The tools they recommend are outlined in Table 1.2. They suggest an assessment of chemotherapy toxicity risk should be undertaken with either the Cancer and Ageing Research Group (CARG) or Chemotherapy Risk Assessment Scale for High-age patients (CRASH) scoring system and they echo SIOG in recommending the VES-13 or G8 screening tool to predict for mortality.

Table 1-2 Geriatric assessment screening tools recommended by ASCO

Domain	Tool
Function	IADLS
Co morbidities	Thorough history or validated tool
Falls	Single question
Depression	Geriatric Depression Scale
Cognition	Mini-Cog Blessed Orientation Memory Concentration Test
Nutrition	Question on unintentional weight loss

Studies have shown the relevance of screening tools for influencing cancer treatment decision making[76]. There is less evidence surrounding whether modifications from the results of the screening change outcomes for the

individual patient. Hamaker et al comment in their systematic review that aspects of the various tools examined can predict for tolerance to treatment and survival but that the results are too inconsistent across different trials for meaningful conclusions to be drawn[77]. Kalsi et al addressed the question of whether intervening based on the results of a geriatric assessment improved overall outcomes for patients by examining tolerance to chemotherapy in patients who were referred to a pilot onco-geriatric service. This cohort study stratified patients pre-chemotherapy into risk groups depending on the results of an initial screening tool (CGA-GOLD). Higher risk patients, according to CGA-GOLD, were referred for a geriatrician-led comprehensive geriatric assessment. The treating oncologist could also refer patients if they raised concerns at their consultation. The primary outcome measures were completion of treatment and grade 3-5 CTCAE toxicity. The study found patients were more likely to complete treatment (p=0.006) and there was a non-significant trend towards lower toxicity rates in the intervention group. There was no difference in overall survival between groups. This was a small study but provided support to the idea of providing geriatrician input for older cancer patients[70].

1.2.7 Geriatric assessment within the neuro oncology cohort

Geriatric assessments have not yet been widely adopted in the neuro oncology setting. Multi-dimensional geriatric assessment has been shown to predict for tolerance to treatment and survival in other tumour types[78,79] however as yet this has not been trialed within the neuro oncology cohort. A large retrospective SEER database study revealed that 21% of GBM patients aged 65 or over spend at least 30 days in hospital following diagnosis and 22% of patients spend at least a quarter of their remaining life in a hospital bed. The risk of extended hospitalization was not related to chronological age alone but instead to comorbidity burden[80]. These figures are similar to an earlier Canadian study showing at least a quarter of GBM patients aged over 60 spent over half of their remaining lives in hospital[81]. Data was not available for a UK cohort. Work in other medical disciplines has shown that a comprehensive geriatric assessment can reduce hospital stay[82]. Similar strategies are urgently needed within this elderly GBM cohort to improve quality of life in the final stages.

A thorough literature review confirms a significant lack of trials focusing on the use of geriatric assessment tools, including the EORTC minimal dataset, in neuro oncology patients. Some studies have tried to use simple stratification techniques or highlighted single aspects of the minimal dataset, as discussed below.

Comorbidities and presenting symptoms

The EORTC minimal dataset includes the documentation of comorbidities using the Charlson Co-morbidity Index (CCI)[83]. The CCI was developed in 1987 as a way of classifying certain comorbidities that may alter the risk for longer term mortality. It is a popular tool within clinical trials as it provides an easy numerical value for more nebulous conditions, and because as it is collected routinely for the Surveillance Epidemiology and End Results (SEER) database in America and therefore is easily accessible.

Fiorentino *et al* retrospectively evaluated patients aged $\geq$ 65 who underwent surgical resection followed by chemotherapy and radiotherapy. They hypothesised that the comorbidity burden would predict for survival and used the Adjusted-Age Charlson Comorbidity Index (ACCI) and the Adult Comorbidity Evaluation-27 (ACE-27) to assess levels of comorbidity. 35 patient records were reviewed and survival data was stratified by ACCI $\leq$ 3 vs >3 and ACE-27 <2 vs $\geq$ 2. ACCI and ACE-27 did not predict for progression free survival but at multivariate analysis ACCI had a significant influence on overall survival (10 vs 22 months for ACCI $\leq$ 3 vs >3, p=0.001)[84]. They go on to report that in their institution, patients are assessed for treatment based on KPS and CCI score rather than age[85].

Chaichana *et al* recorded the individual co-morbidities rather than a CCI index in their retrospective review of pre—operative characteristics of patients aged over 65 years who had undergone surgical resection at their institution, including clinical and operative notes. They controlled for factors known to affect prognosis (extent of resection, use of intraoperative chemotherapy wafers, postoperative chemotherapy or radiotherapy treatment) and found a number of clinical attributes independently associated with decreased survival.

In multivariate analysis, KPS < 80 (RR 1.756 p=0.001), chronic obstructive pulmonary disease (RR 3.762 p=0.01), motor deficit (RR 3.480 p=0.01), language deficit (RR 2.311 p=0.005), cognitive deficit (RR 1.792 p=0.02) and increasing tumour size (RR 1.982 p=0.002), notably tumour size over 4cm, were significant[86].

Tumour location in GBM impacts both on the options for surgical resection and on the symptom burden experienced by the patient. As well as the motor and language deficits seen in Chaichana's study, a large American retrospective review showed that presenting with seizures has been shown to confer an improved prognosis[87,88].

Social situation

The individual social situation of older patients can have a significant effect on their treatment options and decision making. A systematic review in 2015 showed that convenience of treatment has an impact on whether patients will undergo cancer therapy[89]. This is particularly relevant when it comes to radiotherapy, given the requirement for multiple hospital visits. A National Cancer Database review looking at patterns of care of older GBM patients in the USA showed that, as well as having a lower CCI score, living a shorter distance from treatment centre was significantly associated with patients undergoing adjuvant treatment (OR 0.57 p<0.001)[90]. The social support the patient receives also has an effect on survival with a large SEER database study showing that GBM patients who were unmarried presented with larger tumours and were less likely to undergo surgical resection versus biopsy (OR 0.88; 95% CI 0.79-0.98; p = 0.02) or post-operative radiotherapy (OR 0.69; 95% CI 0.62-0.77; p < 0.001) compared to those who were married. Of those who did undergo surgery and radiotherapy, multivariable analysis revealed those who were unmarried still had worse overall survival compared to their married counterparts (HR 1.10; P = 0.003)[91].

G8

The Oncodage screening geriatric eight questions (G8) screening tool was first developed by Soubeyran in 2011 with the aim of providing a way of separating

fitter elderly oncology patients from those who may benefit from CGA[92]. The domains covered include disability, nutrition, cognition, depression, and comorbidities. Scores range from 0 to 17 with scores lower than 14 triggering referral for a CGA.

G8 was validated in the ONCODAGE study where it was tested against full geriatric assessment with sensitivity ranging from 65% to 92% and specificity from 3% to 75%[75,93]. More interestingly, an abnormal G8 score has been shown to be prognostic for functional decline (measured as a decrease in activities of daily living) and overall survival in both newly diagnosed and newly relapsed cancer patients[94,95]. This was performed in all tumour types however due to scarcity of the disease, the number of neuro-oncology patients in these studies was very low.

A recent retrospective study examined the use of the G8 in glioblastoma patients. 89 patients with a new diagnosis of GBM aged $\geq$ 65 between 2010 and 2017 were retrospectively reviewed and their G8 score used to classify them low risk (score 14.5-17), intermediate risk (score 10.5-14) or high risk (score < 10.5) based on the classification validated in a previous study[96]. Patients with a higher G8 score (indicating less impairment) were younger and tended to be more likely to be treated with radio-chemotherapy. On multivariate analysis using abnormal (< 14) vs normal (> 14) G8 score found an abnormal G8 to be associated with poorer survival (hazard ratio [HR]: 10.27; 95% CI: 3.12–33.28; p = .0001). Using the 2 cut off scores as defined in Takahashi et al's study, the median overall survival was 4 months in the low score group, 15 months in the intermediate score group, and 42 months in the high score group. After multivariate analysis, being in the lowest G8 score group was found to remain statistically significant (HR: 55.46; 95% CI: 13.42–229.13; p = .0001) [97]. This is the first use of the G8 tool specifically within the older glioblastoma population but is limited by being retrospective in nature.

Performance status

Performance status has limitations in describing GBM patients as the deficits produced by the tumours can be subtle and not necessarily expressed via

physical disability. Performance status is also highly subjective with studies showing that patients, nurses and doctors will all rate the same patient significantly differently on a performance status scale[98]. However, performance status has historically been used to assess patients for treatment as it is the quickest and best known screening tool.

As early as 2002, Brandes et al recognized that the older patient with GBM represented a vulnerable and undertreated population. They randomized 79 histologically confirmed GBM patients aged over 65 to 59.4Gy in 33 fractions followed by either no chemotherapy, adjuvant PCV or adjuvant TMZ. The groups were well balanced in terms of age and residual disease. In multivariate analysis, the temozolomide arm trended towards improved survival, however the only statistically significant factor was Karnofsky performance status (KPS) [99]. A retrospective population based study examining the outcomes of GBM patients aged 70 or over registered in the French Brain Tumour Database revealed similar results with pre-operative KPS being the only clinically significant prognostic indicator for survival[100].

Curran *et al* used the recursive partitioning analysis technique to look for pretreatment prognostic factors in 1578 patients with high grade glioma who took part in Radiation Therapy Oncology Group trials in the 1970s and 1980s. The aim of the study was to produce prognostic groups to then guide further phase III trials. The authors produced a number of different groups, the main influencing factors being age over 50 and KPS. In addition to those who were older with poorer performance status, they also noted a difference with those who had impaired mental status[101]. The upper age range of this study was 70, reflecting the ages of those enrolled into trials. Scott *et al* continued this method of statistical analysis in 437 patients aged 70 and over pooled from 2 academic institutions. The results were then tested against a separate French cohort of patients for prognostic validation. The authors described 4 groups; patients aged under 75.5 years who underwent surgical resection, those over the age of 75.5 who underwent surgical resection, those with KPS 70-100 who underwent biopsy only and those with KPS less than 70 who underwent biopsy only. These group stratifications revealed significant differences ($p<0.001$) in median

survival when applied to the separate French cohort of 265 glioblastoma patients between the first 2 groups and the third and fourth, however no significant difference between the groups who both underwent surgical resection[102]. The study was limited by its retrospective nature and the lack of input variables including molecular characteristics of the tumours, imaging features and treatment received after surgery however it suggests that chronological age alone should not be used as a prognostic indicator.

Roa et al used age and KPS to determine groups of 'elderly and/or frail' patients in a randomised Phase III trial comparing palliative radiotherapy for GBM of 40Gy in 15# vs 25Gy in 5#. The authors defined this as frail = age $\geq$ 50 and KPS 50%-70%, elderly and frail = age $\geq$ 65 and KPS 50%-70%, and elderly = age $\geq$ 65 and KPS 80%-100%[51]. The rationale behind their classification system is not clear as the formal diagnosis of frailty is based on a far more detailed assessment than KPS. There is controversy as to whether chronological age is an appropriate cut off to use for clinical trials, and, given the work of the NOA-08 and NORDIC studies, you could argue that the 'elderly' group within the IAEA trial were potentially undertreated.

1.2.8 Frailty

The terms frailty assessment and geriatric assessment are sometime used interchangeably however they encompass independently measured domains. Frailty is a term that has been validated within the general geriatric population and is defined as a vulnerability to adverse events as a consequence of physiological decline as part of the ageing process[103,104]. The concept of the 'frailty phenotype' was developed by Fried in 2000. It defines a clinical state, common in older patients, where they are more at risk of poor health outcomes including falls, hospitalization and death[105]. Fried performed baseline assessments in over 5000 patients and found that frailty could be diagnosed if three or more of the following criteria were present: unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity[106].

Within neuro oncology the concept of frailty has been employed by a group at Columbia Presbyterian Hospital who retrospectively examined a surgical cohort of 319 elderly GBM patients, looking for associations between pre-operative factors and the likelihood for resection and risk of complications. They found similar complication rates to studies in younger patient cohorts (21.9% overall rate) and that a low cardiac risk profile, tumour location and high KPS score significantly predicted for more aggressive surgical intervention[107]. In a subsequent paper, the authors went on to retrospectively apply the Canadian Study of Health and Aging Modified Frailty Index to this cohort. The authors studied the case notes of patients aged 65 or over who had undergone resection for glioblastoma. They noted that frail patients were less likely to undergo surgical resection compared to biopsy (odds ratio 0.15; $p < 0.01$), had longer hospital stays (log-rank test for trend, $p<0.01$), and an increased risk of complications (odds ratio 1.40, $p=0.01$). The authors comment on a relationship between frailty score and overall survival however do not account for further treatment in terms of chemotherapy or radiotherapy received within this model[108].

1.2.9 Depression

Depression is one of the leading causes of disability worldwide and in the Western world has an estimated prevalence of between 8% and 16%[109,110]. Depression amongst cancer patients is known to increase with age[111] and the ASCO publication of guidelines to help assess older cancer patients stresses the importance of screening for depression in any geriatric assessment process[13]. Regarding glioma patients, a systematic review of the literature revealed a median frequency of depression of 15% (range 6%-28%)[112]. This has been shown to correlate with poorer outcomes with an increased hazard ratio for death of 1.42 amongst depressed glioma patients[113]. There is very little data available on the use of antidepressants within this patient cohort which is especially important as many of the side effects of anti-depressants are symptoms already experienced by high grade glioma patients[114]. There were also no studies found during this literature review which focused primarily on

older GBM patients and depression, highlighting a need to explore further this important prognostic indicator amongst this cohort.

1.2.10 Neurocognitive deficits

Older neuro oncology patients present a particular challenge due to the location of the tumour. In comparison to other solid tumour sites, the location of a GBM can have a huge impact on a patient's functional status through a central loss of ability rather than secondary to sarcopenia or malnutrition, as are reflected in general geriatric assessment models. There is little data available as to how this impacts on response to treatment or survival. The current screening tool battery suggested by SIOG and ASCO include a short memory screening test however there is little work in the older population on the role of cognitive defects on treatment offered or survival outcomes.

In the large randomised NOA-08 phase III trial baseline and regular mini-mental state examinations (MMSE) were included. The scores of these were well balanced between the two treatment arms and the mean score did not change significantly after treatment. Despite the wide range of scores from 0-30, over 90% of the patients had a MMSE within the normal range. Personal e-mail communication between the researcher and the CI of the study revealed that the MMSE score did not prove significant for survival on univariable analysis. However the recent CCTG CE.6/EORTC 26062 trial showed that a higher baseline MMSE score did predict for improved survival (hazard ratio for death with a 1-unit increase as a continuous variable, 0.96; 95% CI, 0.94 to 0.98; $p<0.001$)[56].

Short screening tools looking for cognitive deficit are by their nature blunt. In younger GBM patients more nuanced work has been carried out looking at pre-treatment cognitive functioning. Meyers *et al* prospectively performed 9 tests including neurocognitive function, quality of life and activities of daily living on 80 patients with relapsed GBM or anaplastic astrocytoma prior to them being enrolled in a phase I or II clinical trial. Although the study was small, the authors found KPS and age to be unrelated to survival, whereas cognitive impairment was a statistically significant prognostic indicator[115]. Impairment in Trail Making

Test b (TMT-b) trended towards correlation with survival in patients with GBM rather than anaplastic astrocytoma. A small study of 50 patients performed by Lee *et al* confirmed the use of TMT-b in consecutive patients undergoing resection for newly diagnosed GBM who had neuropsychological testing pre operatively. TMT-b was the only independent predictor for 6 month progression free survival in multivariate analysis[116].

The work in cognitive functioning was continued by Johnson *et al* who looked retrospectively at 91 patients who had undergone neuropsychological assessment after surgical resection of newly diagnosed glioblastoma. Although subject to the limitations of a retrospective study, they found cognitive impairment to be an independent prognostic indicator, significant even within the subgroups determined by RPA class partitioning. An initial model found a significant relationship between increasing age and greater risk of death ($p<0.001$) however no such relationship with KPS ($p=0.9088$). Within the neuropsychological battery of tests, the Controlled Oral Word Association test and the (TMT-b) were associated with survival both as continuous variables and when analysed as a dichotomous entity[117]. The controlled word association tool test and trail making test are both incorporated into the simple cognitive screening tool the Montreal Cognitive Assessment (MoCA). This adds weight to the theory that KPS is a too crude a tool to measure the significant but subtle impairments glioblastomas can cause.

1.2.11 Conclusion

Treatment regimes in older GBM patients are not yet standardised. There is evidence to support radical concurrent chemotherapy and radiotherapy regimes alongside hypofractionated radiotherapy, with or without concurrent temozolomide or temozolomide alone depending on patient fitness. There are now molecular biomarkers to predict response to treatment in the form of MGMT, however no such clinical markers for fitness for treatment have been standardised. Traditionally chronological age was used as a cut off for offering certain treatments however the aging process is far more complicated than is represented by a single number. Multi-dimensional geriatric assessment is known to predict for survival and toxicity to treatment across other tumour sites.

Within neuro oncology slightly different challenges present themselves in terms of detecting subtle physical and cognitive deficits produced by the tumour themselves. Now that we have multiple different treatment options available for older GBM patients, we should be looking towards developing a feasible and affordable comprehensive assessment tool incorporating the domains of the EORTC minimal dataset alongside neurocognitive reports and pathological biomarkers.

Chapter 2 The influence of clinical and tumour characteristics on survival outcomes for older patients with glioblastoma

2.1 Introduction

Glioblastoma (GBM) is the commonest primary malignant brain tumour amongst the adult population, making up 46% of all malignant brain and CNS tumours and 15% of all primary brain tumours [118]. Incidence rates in the UK are around 4.6/100,000/year which equates to approximately 2,000 cases per year. Incidence peaks in the 65-75 age group with average age at diagnosis being 64. The rates amongst older patients are increasing, with a doubling in incidence in the over 65s between the 1970s and 1990s[8]. As our global population ages it is expected that this trend will continue. GBM has a poor prognosis with median life expectancy of 12-15 months, decreasing to 3-5 months in older patients[7]. This is thought to be due in part to more aggressive tumour biology, in part to under treatment and in part to comorbidities and frailty reducing treatment tolerance.

Standard treatment for those aged under 70 is based on the landmark EORTC trial which randomised patients to radical radiotherapy (60Gy in 30#) alone or with concurrent temozolomide (TMZ) (75mg/m^2 daily) followed by 6 cycles of adjuvant TMZ (200mg/m^2 for 5 days every 4 weeks). An overall median survival benefit of 2.5 months was observed in the chemotherapy arm with 2 year survival of 10.4% in the radiotherapy alone arm compared to 26.5% in the combined treatment arm. 5 year survival improved similarly from 1.9% to 9.8%. This trial recruited patients aged 18-70 and the survival benefit in patients aged over 65 failed to reach statistical significance [38].

Treatment of patients aged 70 or over is not well defined. There is good evidence that radiotherapy improves survival without compromising quality of life when compared to best supportive care however the optimal dose and duration of radiotherapy is yet to be established[47,50,51]. Recent trials have shown

equivalent survival outcomes for patients receiving radiotherapy alone compared to TMZ alone. The 2018 Perry et al trial showed a significant survival benefit from adding concomitant and adjuvant TMZ to hypofractionated RT (40 Gy in 15 fractions). These studies also confirmed the predictive role of MGMT promoter methylation in determining which patients are most likely to benefit from TMZ alone or in combination with radiotherapy[39,55]. The MGMT gene plays a role in repairing DNA damage caused by alkylating chemotherapy agents such as TMZ. Methylation of the promoter region represses gene transcription and increases TMZ sensitivity[119]. IDH 1/2 mutation status has also emerged as a powerful prognostic biomarker. Mutations in the IDH 1 or 2 genes are associated with secondary GBM and with significantly improved prognosis, independent of treatment received[16]. However, IDH mutation frequency is inversely correlated with patient age so this biomarker is less useful in the elderly population [17]. As discussed in an earlier chapter, detailed studies of pathological markers in older GBM populations are rare, so the utility of these and other biomarkers is less clear than in younger patients.

Given the poor prognosis of older GBM patients, there is particular concern over the balance between survival benefits of treatment, which are often small, and treatment side effects and quality of life. Deciding which patients are most likely to benefit from treatment is difficult and no validated tools are currently available. As well as disease specific morbidity, pre-morbid factors play an important part in determining frailty and treatment tolerance. Recursive partitioning analysis has been studied in the older population and four prognostic subgroups were identified based on Karnofsky Performance Status and extent of surgical resection[102]. However there were limitations to the availability of clinical and treatment factors included within this analysis.

The lack of high quality data motivated the researcher to undertake a retrospective cohort study, investigating whether pre-morbid characteristics, disease specific symptoms or tumour imaging features in a cohort of unselected older patients with GBM could predict for overall survival, after accounting for treatment variables. Where archival tumour tissue was available, we undertook a detailed pathological and molecular analysis of these samples, including

repeated histological examination and analysis of the key genetic and molecular abnormalities.

2.2 Methods

2.2.1 Study design

A retrospective, multicentre cohort study, aimed at assessing whether there are pre-treatment clinical, radiological or pathological factors that can predict for overall survival, after accounting for treatment factors.

2.2.2 Study setting

The study was undertaken across three UK NHS centres: The Sussex Cancer Centre (SCC), The Royal Marsden NHS Trust (RMH) and The Beatson West of Scotland Cancer Centre (BWoSCC). Data was collected on all patients diagnosed with a GBM between January 2010 and January 2015. Data was anonymised locally at each site and then collated and analysed centrally by the researcher. Of those patients who underwent surgery, requests were made to each local pathology centre for their archived tissue samples. These were then anonymised by study number locally prior to transfer to the University College London Institute of Neurology (UCL IoN) where central review of the tissue samples was undertaken.

2.2.3 Ethical regulations

Ethical approval was granted from the South Central – Berkshire B Research Ethics Committee, reference number 15/SC0742. The Health Research Authority approval was granted and local research and development agreement in place in all three sites before the study opened. The study was sponsored by Brighton and Sussex University NHS Trust and adhered to Good Clinical Practice research guidelines. A Material Transfer Agreement was in place between each site prior to any transfer of human tissue from the host sites to UCL IoN. No patient identifiable details were sent with the pathology samples. The study was funded by matched grants from The Sussex Cancer Fund, The Beatson Cancer Charity and The Biomedical Research Council.

Further details on ethical approval can be found in Appendix 1.

2.2.4 Eligibility Criteria

All patients aged 70 and over diagnosed with a GBM at SCC, RMH and BWoSCC between January 2010 and January 2015 were included. Diagnosis was made either by histopathological confirmation by a consultant neuropathologist if the patient underwent surgery, or by consensus opinion in the MDM setting based on clinical features and the imaging as reviewed by a consultant neuro-radiologist. The medical records of these patients were screened by the researcher. Patients were excluded if there was uncertainty over their diagnosis or if they were diagnosed at one of the participating centres but their surgery and/or oncology treatment were undertaken elsewhere.

Initially the concept of the 'older' GBM patient was those aged 70 and over as that was the upper age cut off in the Stupp trial published in 2005. However subsequent analysis of the Stupp data has suggested that those aged 65 and over did not receive the same survival benefit as those in the younger age groups and thus the neuro oncology community has tended to use 65 as the age cut off for 'older' GBM patients. There is still some controversy over this however with some UK based neuro oncologists reporting that they treat fitter patients aged between 65 and 70 as per the Stupp protocol whereas others use 65 as a stricter cut off [56]. During the time period of this retrospective study, 70 was more commonly used to classify an 'older' patient cohort and thus the researcher chose this age for eligibility criteria.

2.2.5 Data sources and collection

Patients were identified through local neuro-oncology patient databases, outpatient clinic lists and clinic letters. Those patients who were not seen in outpatient clinics were identified through the electronic NHS Trust records of regional multi-disciplinary neuro-oncology meetings (MDMs). These weekly meetings include neuro-surgeons, neuro-radiologists, neuro-oncologists, specialist nurses and can include physiotherapists, occupational therapists, speech and language therapists and social workers. UK national guidelines state that all patients within the UK with a suspected diagnosis of a GBM should be discussed in their local MDM.

Once a list of patients was collected at each site, details of the patients' clinical and social characteristics, medication history, imaging, and treatment received were gathered from local paper notes, electronic patient records and various NHS databases stored locally.

Where available, the following were recorded for all patients: comorbidities, current medications, marital status, Eastern CoOperative Group performance status (ECOG PS) at diagnosis, presenting symptoms, neurological deficit, tumour location and imaging characteristics, degree of surgical resection, radiation treatment dates and doses and chemotherapy treatment dates and doses. Date of last follow up and, where applicable, date of death were noted.

2.2.6 Clinical characteristics

Comorbidities were classified according to the Charlson Co-morbidity Index (CCI) [83]. The CCI is a validated scoring system based on 19 underlying health conditions with variously assigned weights that are combined into a composite score. The CCI score was calculated by the researcher from the comorbidity history provided by patient letters and MDM discussions. Letters from other clinical specialities were also interrogated to gain as much detail as possible when scoring. The CCI can either be interpreted as a linear variable or by using varying cut off ranges[120]. In this study a cut off value of 3 was used to stratify patients[121].

The number of prescribed current medications was recorded and classified as more or less than 5. Different geriatric screening tools use cut off points between 3-5 to represent significant levels of medications[122,123]. Since the majority of patients in this study were likely to have been started on dexamethasone and a proton pump inhibitor alongside their normal medication, to manage the symptoms of raised intracranial pressure, local neurological symptoms from the tumour itself or post-operative inflammation, a cut off value of 5 was selected to allow for the extra 2 medications.

Data on presenting symptoms were collected. Confusion was documented from either clinic notes or MDM records. This was recorded as a symptom if documented in the clinic consultation or if there was a significantly poor score

on a cognition test such as the Mini Mental State Exam. The use of cognitive screening tools is not yet standard in outpatient clinics and so some flexibility in the documentation of confusion was allowed.

Other neurological symptoms included the presence or absence of seizures as documented in the MDM outcome or clinic notes, hemiparesis (documented on examination in clinic or on the ward), visual disturbance (including double vision and visual field loss) or speech disturbance (classified as expressive dysphasia, receptive dysphasia or slurred speech at examination).

The MDM outcomes in each site were analysed and, where available, ECOG PS data collected. Clinic letters from the first appointment with an oncologist were also interrogated for further ECOG PS details prior to patients starting treatment. The earliest documented performance status after diagnosis was recorded.

2.2.7 Imaging characteristics

Imaging characteristics of the tumours were documented from the consultant neuro-radiologist report of the initial diagnostic MRI scan. Where patients did not have an MRI scan, their diagnostic CT scan was used. Tumours were classified according to whether they were contained within the cerebral hemispheres or were in the corpus callosum, brainstem or cerebellum. It was also noted whether there was documentation of radiological evidence of mass effect or midline shift and whether the initial scans displayed a single focus of visible tumour, multifocal disease or gliomatosis (defined as a diffusely infiltrative glial tumour involving at least three lobes, with or without a discrete mass). These reports were cross referenced with MDM outcomes to check that no subsequent amendments had been made.

2.2.8 Treatment received

Surgery

As described in more detail in earlier chapters, the degree of surgical resection has been shown to correlate strongly with patient outcomes, even in the older GBM population who are arguably more at risk of operative complications. Surgical resection data was therefore collected in this patient cohort from the

operation notes, immediate post-operative MRI scan and MDM discussion. Surgery was categorised as biopsy, subtotal resection (STR) (<90% resected) or gross total resection (GTR) (>90% tumour resected). The definition of a sub total versus gross total resection rates differed across the three trusts. The MDM records and post-operative imaging reports were therefore closely interrogated to ensure that consistency in defining these groups of patients was adhered to. There was no data available on complication rates post-surgery as, in the majority of these trusts, neurosurgery occurred within a different NHS trust to the oncological management and the researcher did not have access to records.

Oncological treatment

Data was collected from computerised radiotherapy records which showed dose and fractionation schedules as well as details on completion of courses. Chemotherapy records were either on paper or computerised depending on the treating NHS Trust. They provided information on type, dosage and number of cycles of chemotherapy received.

These records were then cross referenced with clinic letters and MDM discussions to ensure as much reliability in data collection as possible.

Toxicity data was not collected as this was a retrospective study and no standardised collection method or follow up schedules were applied to this patient group during the study period. The heterogeneity and incompleteness of data that this would have produced was felt to be too significant.

2.2.9 Pathological analysis

It is well documented in younger patients that both MGMT promoter methylation status and IDH 1/2 mutations confer a predictive and/or prognostic effect on patient outcome. The IDH 1/2 mutation and MGMT promoter methylation status were not available for all patients who underwent surgery in this study, as it was not standard practice for these tests to be performed then. Different centres also use different assays to test for MGMT promoter methylation status which may not be equivalent. We therefore undertook repeat pathological testing of all available samples at a central laboratory – UCL IoN.

Samples were dearchived and securely couriered to the lab at UCL IoN. In The BWoSCC the samples are stored at the Glasgow Biorepository. A local review by their neuropathologist was performed in order to ensure tissue blocks with as much representative tumour tissue as possible were sent. Patients with GBM treated at RMH usually have their neurosurgery at St George's Hospital. The neuropathologist at St George's Hospital also performed a local review and suitable tumour samples were sent. At SCC there is no resident neuropathologist so the complete tissue blocks were sent by the laboratory staff.

The following tests were performed:

MGMT promoter methylation

MGMT promoter methylation was tested in two ways. The DNA was extracted and analysed firstly by the methylation sensitive high resolution melting (MSHRM) technique using real time Polymerase Chain Reaction (PCR) and MSHRM software[124]. Subsequently the samples were processed with the MethylationEPIC BeadChip™. Over 850,000 methylation sites were quantitatively interrogated across the genome at single-nucleotide resolution and as part of this an estimate of MGMT promoter methylation was obtained[125]. Results were provided to the researcher by UCL IoN as 'methylated', 'unmethylated' or 'failed'.

IDH 1 and 2 mutation

Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) are metabolic enzymes that catalyse the conversion of isocitrate to α-ketoglutarate, while reducing NADP to NADPH. IDH 1 is located in the cytoplasm and peroxysomes whereas IDH 2 is in the mitochondria. Point mutations in both of these enzymes result in a loss of their normal catalytic activity and the gain of a new function, the production of 2-hydroxyglutarate (D2HG). It is unclear exactly how the biology of the tumour is affected by these mutations, one hypothesis being that the production of D2HG results in genome wide epigenetic changes across the glioma, another that the loss of ability to produce NADPH decreases the oxygen scavenging potential of

the cell, making them more susceptible to damage inflicted by chemo-radiotherapy[126].

Point mutations in both of these enzymes have been associated with defining subsets of low grade glioma and of differentiating between primary and secondary glioblastomas[18].

IDH1 and 2 mutation testing was performed by DNA extraction and purification then real time PCR followed by Sanger sequencing. Results were provided to the researcher by UCL IoN in the categories of 'wild type', 'mutated' or 'failed'.

BRAF V600E mutation

BRAF is a proto-oncogene which encodes a serine-threonine protein kinase B-Raf which plays a key role in growth signal transduction. BRAF V600E mutations are known to be involved in the development of melanoma, colon cancer and papillary thyroid cancer and have been associated with aggressive tumour behaviours and poor prognosis[127]. Their role in the development and progress of glioblastomas is less well known. In paediatric gliomas BRAF V600E mutations are thought to occur in about 13%[128] and appear to confer an improved survival; however this has not been seen in the adult population[129] where incidence is lower at about 5%. There is little data as yet on the impact of BRAFV600E mutations on the elderly primary GBM cohort.

BRAFV600E testing was performed by DNA extraction and purification then real time PCR followed by Sanger sequencing. Results were provided to the researcher by UCL IoN in the categories of 'wild type', 'mutated' or 'failed'.

TERT promoter mutation

The promoter region of the telomerase reverse transcriptase gene (*TERT*) is mutated in around 60-80% of patients with glioblastoma multiforme[130,131]. Mutations most commonly occur at C228T and C250T, around 150 base pairs upstream of the TERT start site. These gain of function mutations provide unrestricted growth properties to the tumour cells by upregulating TERT and thus producing longer telomere lengths. They are associated with older age and appear to confer a poorer prognosis in both primary (IDH wild type) and secondary (IDH mutated) GBMs. Mutation of the TERT promoter region is also

associated with IDH wild type, EGFR amplification, and chromosome 10q loss, but not with MGMT promoter methylation[131].

TERT promoter mutation testing was performed by DNA extraction and purification then real time PCR followed by Sanger sequencing. Results were provided to the researcher from UCL IoN in the format of 'wild type', 'C228T mutation', 'C250T mutation' or 'failed'. As there is no clinical difference known between the effect of a C228T or C250T mutation, these were classed together as 'mutated' versus 'wild type'.

Histone H3 mutation

Histone H3 is one of the five main histone proteins involved in the structure of chromatin making up the nucleosomes. Histone H3 tends to be the most post-translationally modified of the five histone proteins and the most common mutation is H3F3A which codes for histone 3.3. Mutant histone H3.3 disrupts the usual post-translational epigenetic modifications near genes related to brain function and cancer processes. H3F3A mutations are mainly seen in paediatric glioblastomas and those arising in midline locations (pons, thalamus, spine)[132]. Work done in adult patients has shown that the H3F3A mutation seems to be age dependent with adult GBMs showing the wild type unless in a midline GBM[133]. The H3F3A mutation is associated with poorer prognosis[134]. We were interested to see if a larger cohort of older patients would support these findings.

Histone H3F3A mutation testing was performed by DNA extraction and purification then real time PCR followed by Sanger sequencing. Results were provided to the researcher by UCL IoN in the categories of 'wild type, 'mutated' and 'failed'.

PTEN

Phosphatase and tensin homolog (*PTEN*), located on chromosome 10q23.3, is a tumour suppressor gene, playing an important role in controlling cell proliferation, invasion, adhesion, apoptosis and DNA damage repair. It is commonly down-regulated or lost in prostate, breast and brain tumours. In gliomas, the loss of PTEN expression has been shown to be an early event with

deletion mutations occurring in between 5% and 40% of cases[135]. PTEN mutations have been shown to confer a worse prognosis in GBM patients[136].

PTEN mutations were analysed using quantitative real time PCR with preassessed Taqman probes for analysis of copy number changes in the PTEN gene. Results were provided to the researcher by UCL IoN in the format of PTEN 'loss', 'retained' or 'failed'.

EGFR

Epidermal Growth Factor Receptor (EGFR) belongs to the larger family of HER receptors with tyrosine kinase activity. EGFR is overexpressed and/or hyperactivated in about 60% of primary GBMs versus only around 10% of secondary[137]. In older patients, small studies have shown that overexpression of EGFR is an independent predictor of prolonged survival in patients aged over 60[135]. We wished to assess whether this continued to be true amongst a larger group of those aged over 70.There have a been an number of clinical studies examining the use of small molecule EGFR receptor and pathway inhibitors but with conflicting results and no clear survival benefit as yet[138].

EGFR mutations were analysed using quantitative real time PCR with preassessed Taqman probes for analysis of copy number changes in the EGFR gene. Results were provided to the researcher by UCL IoN in the format of 'no amplification' (score of 2-5), 'weak amplification' (score 6-24), 'moderate amplification' (score 25-45) or 'strong amplification' (score >45).

2.2.10 Statistical analysis

Descriptive statistics were used to outline the cohort characteristics and illustrate the treatment schedules received. Date of diagnosis was taken as the date of the first brain scan showing classic radiological features of a GBM, to enable consistency between those patients diagnosed radiologically and those who subsequently had surgery and histopathological corroboration. Overall survival was calculated from date of diagnosis to time of death from any cause, or last follow up. Patients lost to follow up or still alive were censored. Median survival of the cohort, with 95% confidence interval, was determined using the Kaplan-Meier method.

Differences between groups were analysed using chi-square testing. In order to investigate relationships between pre-morbid and tumour characteristics and survival outcome, univariable analysis of overall survival was performed using the Cox proportional hazards method to produce unadjusted hazard ratios with 95% confidence intervals. The assumptions for proportional hazard testing were met. The covariates included demographic details, ECOG performance status, comorbidities and current medications, presenting symptoms, radiological characteristics and treatment received. Kaplan Meier survival curves were produced for those covariates with significant hazard ratios. All factors were then included to generate a multivariate Cox proportional hazard regression model and backward stepwise selection used to refine this model. Statistical significance was determined by a 2-sided *P* value of $\leq$ 0.05. All analyses and calculations were performed using SPSS v22.

The cohort was initially analysed without the pathological data which only became available at a later date. This analysis was published in the peer reviewed journal Clinical Oncology[88] (see Appendix 3).

2.3 Results

2.3.1 Patient characteristics

In total, 339 patients were identified as meeting the eligibility criteria across the three sites. In keeping with published literature, GBMs in this cohort were slightly more common in men with a male to female ratio of 1.31:1. Median age at diagnosis was 75 (range 70-90). At the time of diagnosis 225 (69%) of patients were performance status 0-2. 314 (97%) patients had a CCI less than or equal to 3 and 150 (46%) were taking 5 or fewer medications. The baseline characteristics are outlined in Table 2.1.

241 (71%) patients had an MRI scan at diagnosis with regional variation in scanning patterns. 9 patients were classified by the MDM as having 'gliomatosis cerebri'. This term was previously used to describe an infiltrating high grade glioma which involved multiple contiguous lobes of the brain – at least 3 according to the 2007 WHO CNS classification. However the 2016 updated WHO classification no longer recognises gliomatosis as a distinct pathological entity, instead describing it as a particular pattern of growth, and the term has recently fallen out of favour[139]. This data was collected prior to the publication of the updated WHO classification and so still contains the term.

230 (68%) of patients met a neuro-oncologist in an outpatient setting compared to 109 (32%) who were discussed at an MDM and managed by their neurosurgical teams, inpatient medical teams or acute general oncology alone and subsequently received only best supportive care. 250 (74%) patients were offered a referral to palliative care services at some stage of their treatment.

Table 2-1 Baseline patient demographics

Variable		N (%) [a]
Age [b]		75 (72-79)
Age Range		70-90
Age group:	70-74.9	146 (43)
	75-79.9	111 (33)
	80-84.9	56 (17)
	85-89.9	25 (7)
	≥ 90	1 (<1)
Gender:	Male	192 (57)
	Female	147 (43)
ECOG performance status [b]		2 (1-3)
ECOG performance status:	0	23 (7)
	1	105 (31)
	2	97 (29)
	3	75 (22)
	4	27 (8)
	Not recorded	12 (3)
Marital status	Single	92 (27)
	Partner	186 (55)
	Not recorded	61 (18)
Charlson comorbidity index	≤ 3	314 (97)
	> 3	9 (3)
Comedications	< 5	150 (46)
	≥ 5	173 (54)
Presenting symptom	Confusion	127 (38)
	Partial/full hemiparesis	118 (35)
	Speech disturbance	114 (34)
	Seizures	94 (29)
	Visual disturbance	29 (9)
Location	Hemispheric	310 (91)
	Left sided	128 (38)
	Right sided	171 (50)
	Bilateral	40 (12)

Variable		N (%) [a]
Focality	Single focus	246 (73)
	Multifocal	84 (25)
	Gliomatosis	9 (3)
Pressure	Mass effect	199 (60)
	Midline shift	139 (42)
Seen by a neuro-oncologist in clinic	Yes	230 (68)
	No	109 (32)

[a] unless stated [b] median (IQR)

2.3.2 Treatment

176 (52%) patients underwent a surgical procedure (Table 2.2). Of these 68 (39%) had a biopsy, 71 (40%) had a STR and 37 (21%) had a GTR. Of those patients who had surgery, over a third subsequently received only best supportive care.

122 (36%) patients received radiotherapy. 22 (18%) of these had a radiological rather than a histological diagnosis of GBM. Of the 122 patients, 18 (15%) patients were treated with 60Gy in 30# of radiotherapy with concurrent TMZ (75mg/m^2 daily) followed by adjuvant TMZ (200mg/m^2 for 5 days every 4 weeks). 15 (83%) of patients completed their concomitant regime. 3 (17%) patients completed the course of radiotherapy but stopped the TMZ prior to the end of the concomitant regime due to fatigue. Of the 15 who completed concomitant TMZ, 12 continued to adjuvant TMZ. All of these patients received at least 2 cycles of adjuvant TMZ and 4 (25%) completed all 6 cycles. The rest halted due to either progression or fatigue.

6 (5%) patients were treated with radical radiotherapy alone with regimes of at least 54Gy. The majority of patients who received radiotherapy treatment received a palliative regime with 94 (77%) completing 30Gy in 6# and 3 (2%) patients 40Gy in 15#. 1 patient was treated with a twice daily regime of 45Gy in 20#, however this was stopped after 14# due to fatigue. 22 patients were treated with palliative radiotherapy on the basis of the radiological diagnosis,

without having undergone surgery. The publication of work from the IAEA[50] and more recently the NCT00482677 Perry trial[56] have helped to established 40Gy in 15# as a more usual palliative regime however at the time of this data collection 30Gy in 6# was a much more common schedule, particularly in the UK.

51 (15%) patients received chemotherapy. 18 were treated with concurrent radiotherapy and TMZ, 16 with single agent TMZ as first line treatment and 1 with single agent lomustine as first line treatment.

Reflecting the lack of standardised clinical guidelines for this patient group, follow up varied depending on the oncology centre, the treatment involved and the general condition of the patient. Patients with poor performance status who were not fit for treatment were often seen initially by a neuro-oncologist and then subsequently managed in the community or palliative care settings. Those patients who underwent radical or high dose palliative treatment were generally followed up on a three monthly basis if it was felt they would be fit for second line treatment at time of progression.

13 patients received TMZ, 2 patients lomustine alone and 1 patient combination chemotherapy with procarbazine, lomustine and vincristine as second line treatment.

Table 2-2 Initial treatment received

Variable		**N (%)**
Surgery	None	163 (48)
	Biopsy	68 (20)
	Subtotal resection	71 (21)
	Gross total resection	37 (11)
Oncological treatment	Best supportive care	202 (60)
	Palliative radiotherapy	91 (27)
	Radical radiotherapy	6 (2)
	Concurrent CRT	18 (5)
	TMZ alone	21 (6)
	Lomustine alone	1 (<1)

2.3.2 Pathological markers

A number of the 176 patients who had surgery only underwent biopsy and on pathological re-examination there was insufficient tissue for retesting. At St George's hospital, 30 patients underwent surgery but only 10 samples were adequate for reanalysis. At Brighton and Sussex NHS Trust 39 had surgery but only 17 were suitable and in Glasgow 91 patients had surgery whilst 51 were suitable for reanalysis. 78 samples therefore underwent pathological processing and molecular analysis at UCL IoN (Figure 2).

MGMT methylation status was available in 96% of patient samples. The prevalence of MGMT promoter methylation appears to be independent of age and, consistent with the published literature, 45% of this cohort showed methylation of the MGMT promoter region[21]. Since the publication of the new WHO guidelines for classification of GBMs in 2016[18], IDH 1 mutations are now recognised as a marker to distinguish between different types of GBM. Glioblastoma - IDH-mutant, tend to have evolved over time from lower grade astrocytomas and are sometimes called 'secondary GBMs'. They more commonly present in younger patients. Glioblastoma - IDH wild type, or 'primary GBMs' have arisen de novo and tend to present in older patients and have a more aggressive behaviour pattern with associated poorer prognosis. All patients pathologically examined in this cohort had Glioblastoma – IDH wild type tumours.

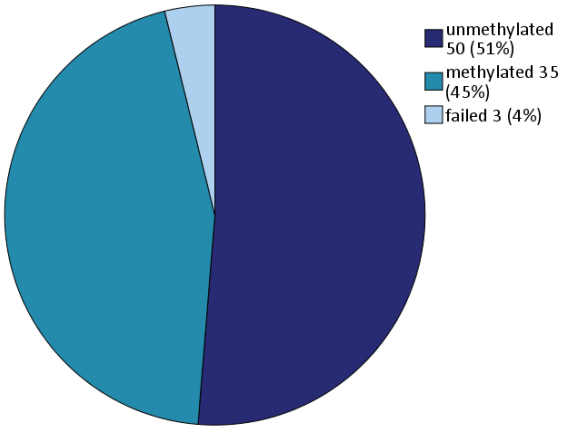
BRAF V600E mutations are present in around a quarter of paediatric glioblastomas and become less common as people age. We have shown here that in the older patient cohort there is no evidence of BRAF V600E mutations in the 89% of patients who had tissue that was successfully analysed.

The analysis of TERT mutations was problematic at UCL IoN leading to high failure rate (54%). Of those who had successful results, 83% showed a mutation in the promoter region of the TERT gene, in line with published literature. There were no H3F3A mutations found in our cohort, again in line with published literature[24].

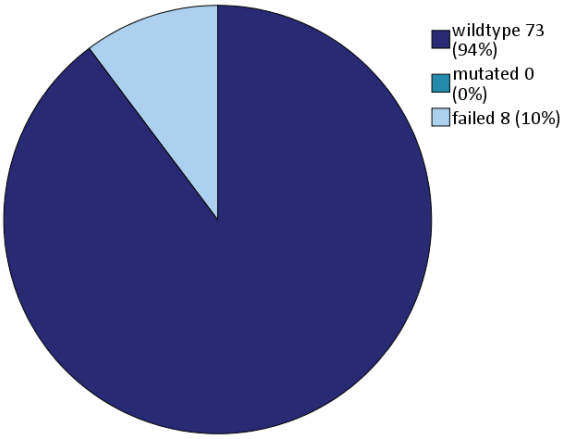
Loss of PTEN has previously been described in 5-40% of adult GBMs; our cohort showed a higher rate at 63% which may reflect the older age range of this cohort compared to other ‘adult’ studies. EGFR overexpression has been noted previously in the literature at around 60%. Our cohort had a slightly lower rate at 39%.

2.3. Figure 2 Pathological markers (original in colour)

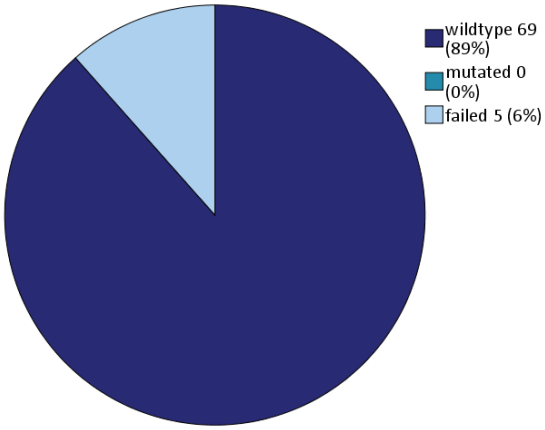
MGMT promoter methylation



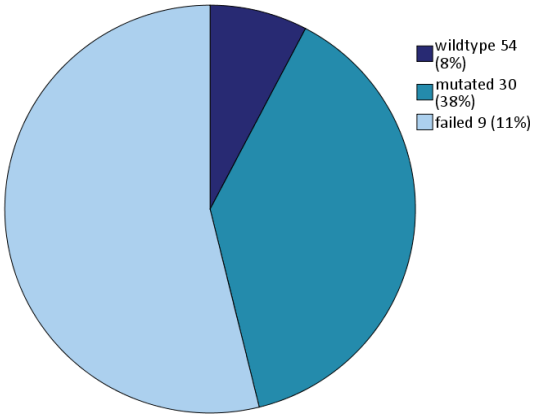
IDH1 mutation



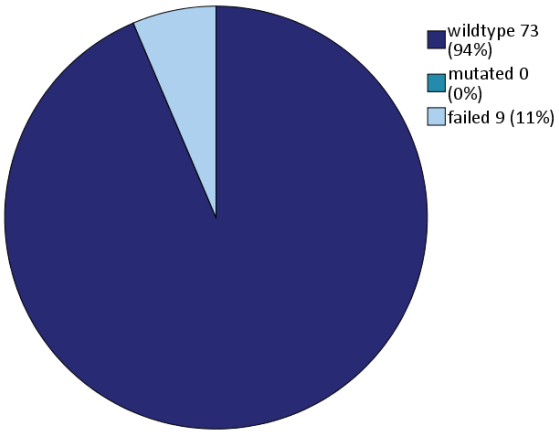
BRAF V600E mutation



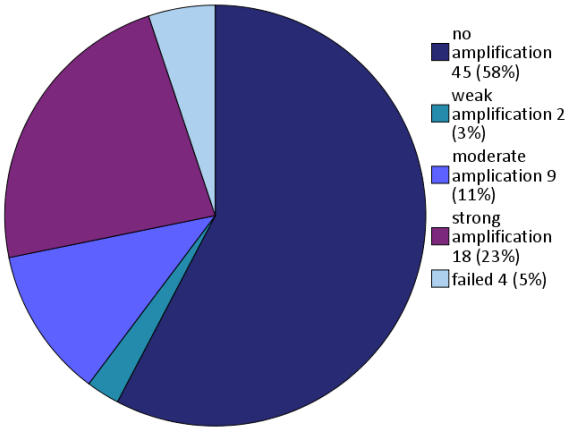
TERT mutation



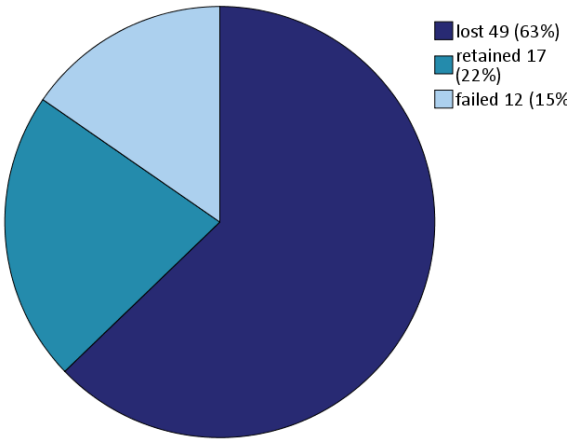
H3F3A mutation



EGFR amplification



PTEN



3 Survival

Censoring was performed in January 2016 and at that point 323 patients (95%) had died. Median overall survival in the whole group was 3.8 months (range 0.1 – 62 months; 95% confidence interval 3.3 - 4.3 months). The probability of survival at 3, 6, 12 and 24 months was 62%, 34%, 13% and 4% respectively.

Univariable analysis

To investigate a relationship between individual factors and overall survival, univariate analysis was performed using Cox regression analysis (Table 2.3). Patients aged 75-90 had a statistically significant increased risk of death compared to those aged 70-75. This trend did not carry forward into those aged

90-95, however the very small numbers in this group are likely to have affected the significance of these results.

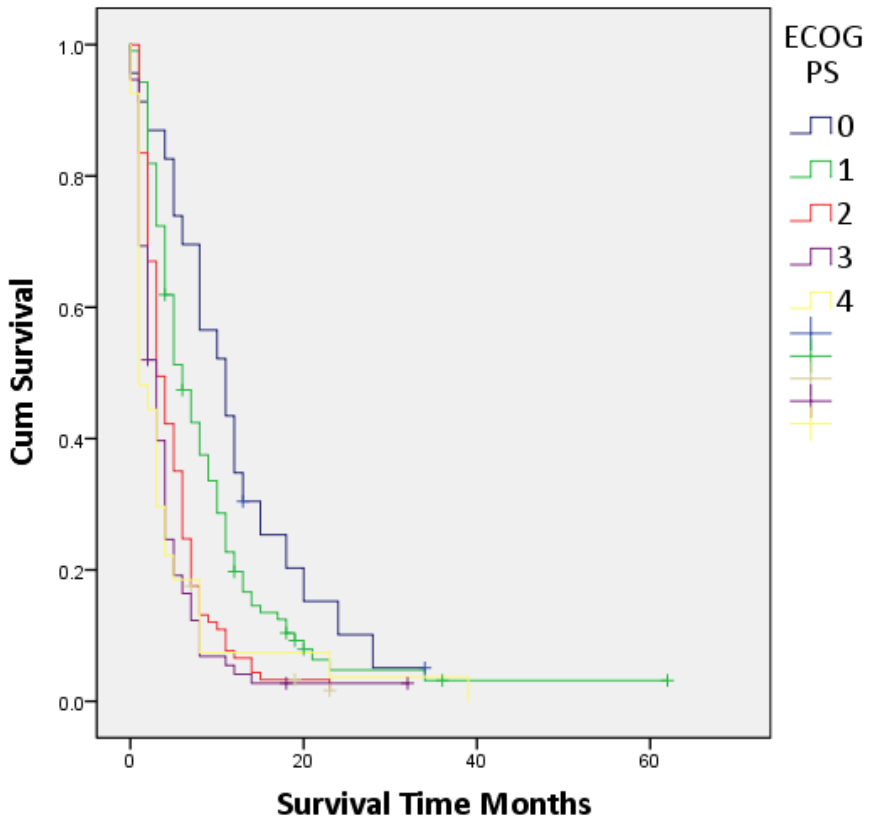
Table 2-3 Univariable survival analysis

Variable		Hazard ratio	95% CI	*p*-value
Age range (compared to 70-74)	**75-79**	**1.34**	**1.03-1.72**	**0.03**
	80-84	**1.88**	**1.36-2.58**	**0.00**
	85-89	**2.15**	**1.39-3.32**	**0.00**
	> 90	3.60	0.50-25.91	0.20
Gender	Female	0.97	0.78-1.21	0.79
ECOG PS (compared to 0)	1	1.41	0.88-2.27	0.15
	2	**2.27**	**1.41-3.67**	**0.00**
	3	**2.93**	**1.80-4.80**	**0.00**
	4	**2.83**	**1.59-5.03**	**0.00**
Marital status	Partner	0.89	0.69-1.15	0.38
CCI	> 3	0.69	0.34-1.41	0.31
Comedications	> 5	1.12	0.85-1.33	0.15
Seizures	**Present**	**0.64**	**0.50-0.82**	**0.00**
Confusion	**Present**	**1.34**	**1.09-1.72**	**0.01**
Hemiparesis	Present	1.19	0.94-1.49	0.15
Visual disturbance	Present	0.96	0.66-1.41	0.84
Speech disturbance	Present	1.19	0.94-1.50	0.16
Hemispheric (compared to brainstem/cerebellum)	**Yes**	**0.65**	**0.44-0.96**	**0.03**
Focality (compared to single focus)	Multifocal	0.97	0.75-1.25	0.80
	Gliomatosis	0.82	0.41-1.66	0.56
Side (compared to left)	**Right**	**0.77**	**0.61-0.98**	**0.03**
	Bilateral	1.17	0.81-1.69	0.40
Midline shift	Present	1.12	0.90-1.40	0.32
Mass effect	**Present**	**1.25**	**1.02-1.57**	**0.05**
MGMT	Methylated	0.66	0.40-1.07	0.09

Variable		Hazard ratio	95% CI	*p*-value
TERT	Mutated	2.22	0.77-6.46	0.14
PTEN	Retained	0.63	0.36-1.13	0.12
EGFR	Overexpressed	0.85	0.52-1.39	0.51
Surgery (compared to none)	**Biopsy**	**0.61**	**0.45-0.81**	**0.00**
	STR	**0.47**	**0.35-0.64**	**0.00**
	GTR	**0.35**	**0.24-0.52**	**0.00**
First treatment (compared to BSC)	**Pall RT alone**	**0.47**	**0.36-0.61**	**0.00**
	TMZ alone	**0.28**	**0.17-0.46**	**0.00**
	Chemo-RT	**0.17**	**0.10-0.30**	**0.00**
	CCNU alone	0.74	0.10-5.26	0.76
	Radical RT alone	**0.34**	**0.14-0.84**	**0.02**

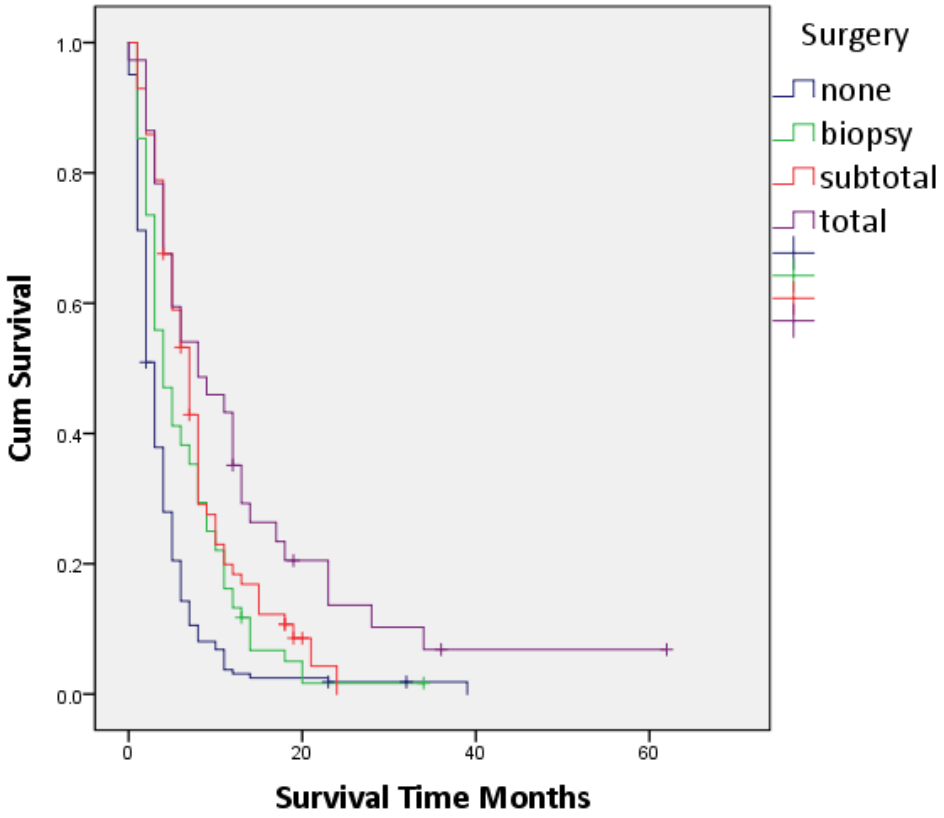
ECOG performance status greater than 1 (Figure 3), presenting with confusion (p=0.01, HR 1.34) and the presence of mass effect on the diagnostic scan (p=0.05, HR 1.25) were significantly associated with an increased risk of death. Presenting with seizures (p=0.00, HR 0.64), right sided tumours (p=0.03, HR 0.77) and tumours confined to the cerebral hemisphere (p=0.03, HR 0.65) were significantly associated with improved survival.

Figure 3 Overall survival according to performance status (original in colour)



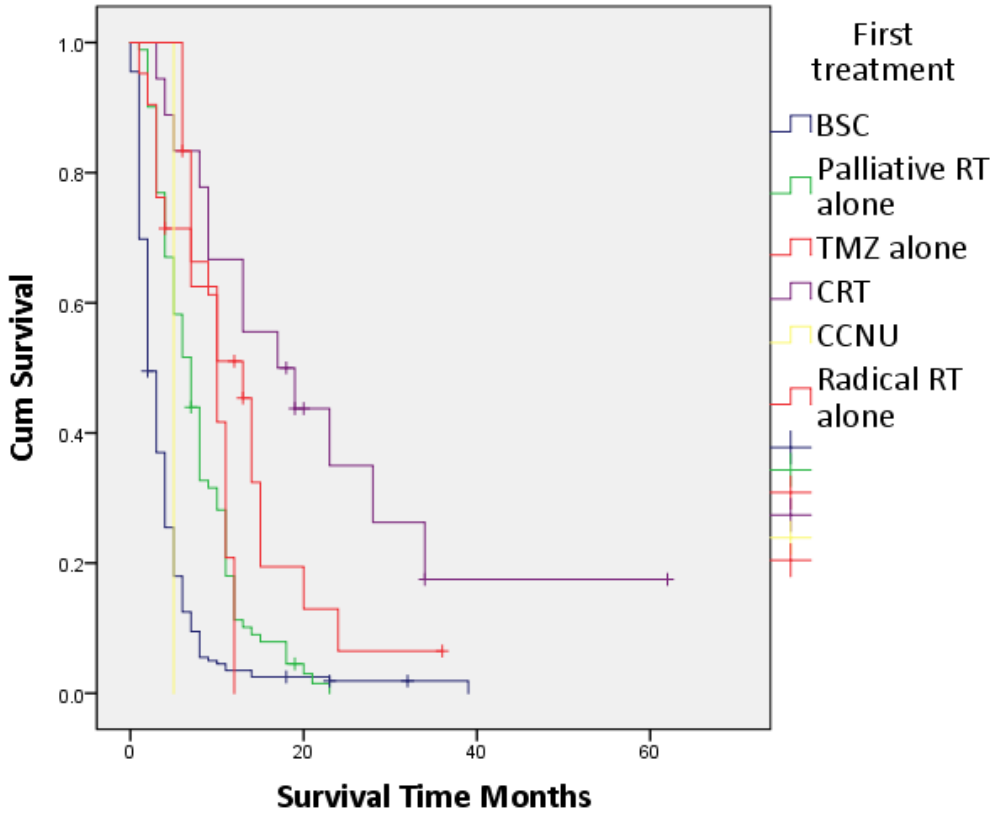
In assessing the effect of treatment received, patients who underwent surgery had a statistically significant improvement in survival which was proportional to the degree of resection performed (Figure 4). Median overall survival in those without surgery was 3.0 months (IQR 1.0-5.0 months), compared to 4.0 months (IQR 2.0-9.0 months) for biopsy, 7.0 months (IQR 4.0-10.0 months) for subtotal resection and 8.0 months (IQR 4.0-17.0 months) for total macroscopic resection.

Figure 4 Overall survival according to surgery received (original in colour)



Those who received active oncological treatment (radiotherapy and/or chemotherapy) had a decreased risk of death. Median overall survival for those offered only best supportive care was 2.0 months (IQR 1.0.-5.0 months) compared to 7.0 months (IQR 4.0-11.0 months) for palliative radiotherapy, 13.0 months (IQR 4.0-15.0 months) for single agent TMZ, 10.0 months (IQR 7.0-11.0 months) for radical radiotherapy and 17.0 months (IQR 9.0-34.0 months) for radical chemo-radiotherapy (Figure 5).

Figure 5 Overall survival according to primary oncological treatment (original in colour)



Multivariable analysis

In the multivariate analysis, pre-treatment characteristics predicting for overall survival that remained significant included ECOG performance status, presenting with seizures, tumours confined to the cerebral hemisphere and radiological evidence of multifocal tumours or gliomatosis (Table 2.4).

As ECOG performance status worsened from 0 to 4, the hazard ratio for death also increased in a stepwise fashion. ECOG PS 1 approached significance with a hazard ratio of 1.60 (p=0.06). However PS 2 conferred a 67% increased risk of death compared to PS 0 (p=0.05), ECOG PS 3 conferred a 98% risk increase (p=0.02) and ECOG PS 4 a 111% risk increase (p=0.05). Presenting with seizures conferred a protective influence with a decreased risk of death of 35% (p<0.01). Similarly, presenting with a hemispherically located tumour decreased risk of death by 38% (p=0.05). This was independent of surgery received.

Presenting with multifocal disease or gliomatosis compared to a single focus of visible disease on the diagnostic CT or MRI scan was significantly associated

with increased risk of death in multivariable analysis. This was not significant in univariable analysis however there was a significant relationship between focality and surgery received. Those patients with multifocal disease or gliomatosis were less likely to receive any form of debulking surgery (chi^2 p=0.02). Removing either of these variables significantly worsened the fit of the multivariable model.

The extent of surgery was significantly associated with a decreased risk of death for subtotal or total tumour resection compared to no surgery. Undergoing a subtotal resection decreased the risk of death by 32% (p=0.05) and a total tumour macroscopic resection decreased risk by 65% (p=0.04) compared to no surgery.

After accounting for surgery, the risk of death was decreased significantly with most active treatment options. Palliative radiotherapy decreased risk of death by 40% (p=0.01), TMZ alone by 58% (p=0.01) and radical chemo-radiotherapy by 80% (p<0.01). The use of radical radiotherapy alone or lomustine chemotherapy alone were not statistically significant. This is potentially due to low numbers of patients in these groups; 6 and 1 patients respectively.

MGMT promoter methylation status was not significant on univariable analysis. The researcher would have suspected a relationship between MGMT promoter methylation status and being offered first line single agent temozolomide or chemo-radiotherapy however this was not found to be significant (chi^2 p=0.78) and MGMT status was not included in the multivariate model. Of the 10 patients who received single agent temozolomide and had MGMT promoter methylation testing, there were 4 methylated and 6 unmethylated. Of the 11 who received chemo-radiotherapy and had MGMT promoter methylation testing, there were 7 methylated and 4 unmethylated. The numbers are therefore very small in terms of identifying the predictive effect of MGMT promoter methylation status in these treatment arms.

Table 2-4 Multivariable survival analysis

Variable		Hazard ratio	95% CI	*p*-value
ECOG PS (compared to 0)	1	1.60	0.98-2.61	0.06
	2	**1.67**	1.01-2.82	**0.05**
	3	**1.98**	**1.11-3.53**	**0.02**
	4	**2.11**	**1.01-4.40**	**0.05**
Seizures	**Present**	**0.65**	**0.49-0.86**	**0.00**
Hemispheric	**Yes**	**0.62**	**0.37-0.99**	**0.05**
Focality (compared to single focus)	**Multifocal**	**0.65**	**0.48-0.89**	**0.01**
	Gliomatosis	**0.35**	**0.14-0.91**	**0.03**
Surgery (compared to none)	Biopsy	0.88	0.61-1.25	0.47
	STR	**0.68**	**0.46-1.00**	**0.05**
	GTR	**0.61**	**0.38-0.98**	**0.04**
First treatment (compared to BSC)	**Pall RT alone**	**0.60**	**0.41-0.86**	**0.01**
	TMZ alone	**0.42**	**0.22-0.77**	**0.01**
	Chemo-RT	**0.20**	**0.10-0.42**	**0.00**
	CCNU alone	1.98	0.25-15.68	0.52
	Radical RT alone	0.47	0.18-1.22	0.12

2.4 Discussion

The treatment of older patients with GBM remains a contentious topic. Since the EORTC trial of 2005, the academic community has recognised a dearth of evidence amongst this cohort. The number of prospective trials within this group remains low, however radiotherapy schedules have been examined notably in the trials by Keime-Guibert[47] and subsequently by the International Atomic Energy Agency[50,51]. The role of single agent temozolomide has been explored with the publications of the NOA-08[55] and NORDIC[39] studies. Since this retrospective study was performed, the publication of the NCT00482677 trial by Perry et al, examining hypofractionated chemoradiotherapy regimes using 40Gy in 15# with or without concurrent and adjuvant temozolomide has established a new treatment paradigm for GBM the over 65s[56]. The difficulty remains in deciding, when faced with an older patient recently diagnosed with a GBM, whether they would be fit enough to withstand the toxicities associated with the treatment options available and therefore gain the associated conservative survival benefit without a significant impact on quality of life.

There has been recent international focus on older patients with cancer[12] with many studies across different tumour groups looking at embedding detailed assessments of older patients within the outpatient setting. The 'geriatric assessment' is a holistic approach to examining the older patient, looking at domains including social situation, mobility, co-morbidities, cognition, fatigue and nutrition. It has been shown to predict for tolerance to treatment and overall survival[67,69]. No such work has yet been done within the neuro oncology arena. This study aimed to explore whether retrospectively analysed pre-treatment clinical, pathological and radiological characteristics could predict for survival.

This study collected comorbidities using the Charlson Comorbidity Index. The CCI was originally derived for hospitalized patients in general medicine, but revised versions have since been validated in multiple patient populations. In oncological patients the score for cancer is not given for their primary disease. Our study did not reveal a relationship between CCI score and overall survival however retrospectively calculating the CCI score can result in underreporting

and only 3 patients in our cohort had a CCI score over 3 which is lower than we would have expected. The number of comedications was similarly not significant. Although it is a crude scoring system, ECOG PS[140] is commonly used as a way of classifying patients for treatment decisions in oncology and is more routinely available than detailed assessment tools. Our study recorded performance status measured at baseline in 97% of patients and this remained a significant factor for survival on multivariable analysis.

A Canadian retrospective study by Bawa et al published in 2011 looked at retrospective factors contributing to survival in GBM patients aged ≥65 showed presenting with seizures conferred an improved prognosis[87]. This was confirmed amongst the slightly older population in our study and may potentially be due to these patients presenting earlier on in their disease course and having escaped significant other neurological deficits.

A large Surveillance, Epidemiology and End Results (SEER) database study performed in 2005 revealed a link between marital status and survival in patients with GBM. Those who were unmarried presented with larger tumours and were less likely to undergo surgical resection versus biopsy (OR 0.88; 95% CI 0.79-0.98; $p = 0.02$) or post-operative radiotherapy (OR 0.69; 95% CI 0.62-0.77; $p < 0.001$) compared to those who were married. Of those who did undergo surgery and radiotherapy, multivariable analysis revealed those who were unmarried still had worse overall survival compared to their married counterparts (HR 1.10; $P = 0.003$)[91]. Marital status did not prove to be significant in our study however collection of data on this point was difficult from the clinical notes and we were missing data on almost a fifth of patients.

Radiological assessment by an experienced neuro-radiologist can provide prognostic information. As shown, patients with a tumour located outside of the cerebral hemispheres, evidence of mass effect and multifocal disease or gliomatosis on their diagnostic scan have poorer outcomes. The presence of more than a single focus of disease on a scan correlated with a decreased chance of surgical debulking although the other factors were independent prognostic indicators.

The main prognostic factors previously used to stratify GBM patients have been age and performance status[101]. This study showed that increasing age was not significant when performance status and treatment factors were accounted for. In line with other studies, patients treated with surgical debulking had improved outcomes compared to those with biopsy or no surgery[36,141]. Similarly those patients treated with radical chemoradiotherapy had the greatest survival benefit of all treatment modalities. This supports the argument that chronological age alone should not be used to determine treatment offered as it is a poor representative of physiological reserve[66,142].

Analyses of the molecular landscape of GBMs have revealed significant differences in tumours from younger and older patients. This cohort of patients had samples re-examined in a central lab which confirmed that all the patients had GBM – IDH wildtype tumours. This study supports the conclusions other authors have drawn that BRAFV600E mutations and H3F3A mutations are less common in older patients. TERT mutations have previously been shown to confer poorer prognosis in patients aged over 60 however there was no evidence of this within our cohort with no significant relationship seen on univariable analysis with Cox regression. This may be due to the high failure rate in processing of TERT mutations leading to small numbers of samples. MGMT promoter methylation rates were consistent with the published literature however the prognostic effect described in other studies were not present in our cohort. This may be due to the relatively small number of patients who had MGMT promoter methylation testing performed and the wide variety of treatment schedules they subsequently undertook. EGFR has been a target for therapeutic use amongst other cancer types, however as yet there have been no significant trials showing effective use within the GBM setting[143]. The positive prognostic effect of EGFR amplification amongst older patients which has previously been described[23] was not seen in our cohort however this may be due to lower than normal rates of amplification within our group compared to similar cohorts[144]. The rate of PTEN loss within this group was higher than has been previously described and the poor prognosis that it has been shown to confer was not present. However, studies that have previously described this

have been mainly observational in nature rather than randomised prospective clinical trials[136]. The ongoing molecular analysis of GBM samples throughout clinical trials has provided hope for a targeted therapy approach to treatment. This has, as yet, been relatively unfruitful, potentially due to the intra- and inter-tumoural heterogeneity of GBMs, both temporally and spatially, making it hard to identify driver mutations. The location of GBMs and relative lack of extra-cranial metastases also makes repeated biopsies impractical[145].

Although this is a retrospective series, its large size and multicentre approach has produced findings that may provide some guidance for evaluating which patients derive more benefit from more aggressive treatment. The survival data from this study is in line with national database interrogation[7] however this study provides more detailed clinical information than is available via national databases and is, to the authors' knowledge, the largest UK based retrospective review incorporating details of clinical presentation, co-morbidities and imaging characteristics within the older cohort of GBM patients. To avoid selection bias, all patients with the diagnosis of GBM during the study period were included, irrespective of treatment received. This enabled an overall survival to be calculated which is representative of the true state of older GBM patients within the UK rather than only those who were well enough for an operation and histopathological diagnosis.

This study is subject to the limitations common to all retrospective reviews, including inadequate documentation from hospital and clinic notes however detailed examination of all records available has resulted in only small amounts of missing data which is a strength of this particular retrospective review. Thus treatment related toxicities were not assessed due to a lack of consistent information.

2.5 Conclusion

Older patients with GBM remain an under researched population and continue to have a poorer prognosis than their younger counterparts. Treatment options are available within this cohort however the clinical assessment and treatment decision making remains unstandardised. This study shows performance

status, clinical presentation and imaging characteristics are prognostic for survival outcomes, irrespective of age or treatment received. Further work is needed to provide detailed prospective assessments of older GBM patients, embedding a multi-disciplinary neuro-oncology specific geriatric assessment within the oncology outpatient setting. This would enable the development of clinical, radiological and biological prognostic and predictive biomarkers within this vulnerable population.

Chapter 3 Survey of current UK neuro-oncology practice for older GBM patients

3.1 Introduction

Glioblastoma (GBM) is a rare condition however the incidence increases with age, with a mean age of diagnosis of 64 and incidence peaking in the 7th and 8th decades of life[7,146]. Despite this, the majority of clinical trials were performed in those aged under 70 years and thus treatment regimens are not standardised in elderly cohort. Older patients have a poorer prognosis and treatment is generally aimed at palliation rather than cure. It is vital that the correct treatment decisions are made in order to balance quality of life and treatment associated toxicities with the potential survival benefit.

Elderly GBM patients provide a unique clinical scenario due to the complexity of distinguishing neuro oncology related symptoms from general frailty. Assessment of older patients with GBM is challenging and it can be difficult to predict which patients will benefit from active treatment. Multi-dimensional geriatric assessment has been shown to predict for tolerance to treatment and survival in other tumour types[78]. It is apparent that the assessment tools used in oncology patients with extra-cranial malignancies are likely to be less valid within the GBM cohort because of the unique and potentially isolated deficits caused by the disease itself. As yet there is a paucity of trial data assessing the benefit of geriatric assessment in determining treatment options and providing a prognostic scoring system amongst elderly neuro oncology patients.

Due to the lack of consensus on standard of care within this population, a starting point for designing tools to help assess older GBM patients is to provide an insight into current clinical practice across the UK. In order to inform the design of the prospective feasibility study described later in this thesis, we here present the results of a cross sectional survey of all practicing neuro oncology consultants in the UK, aiming to investigate current assessment techniques and prescribing practices.

This study was published in the peer reviewed Journal of Geriatric Oncology. See Appendix 3 for the complete manuscript.

3.2 Methods

3.2.1 Study design

A cross sectional study was performed using an online questionnaire designed using the SurveyMonkey™ tool. The questionnaire was designed by the investigator and the validity of the questions assessed by 3 consultant co-investigators from 3 different centres. Some modifications were applied to the questionnaire before it was sent to the wider population. There is no standardised age cut off for what constitutes an 'elderly' oncology patient. Within neuro oncology the landmark EORTC trial by Stupp et al in 2005 which standardised chemo-radiotherapy as the standard of care was performed in patients aged up to 70[38]. Although the survival benefit was not reached in the 65-70 age group, neuro oncologists have used the Stupp protocol in older patients. Since this cross sectional study was performed, the trial by Perry et al using hypofractionated concurrent chemoradiotherapy in those aged over 65 has been published, providing further treatment options for those in the older age group[56]. However, the investigator was interested in the approach of UK based consultant neuro-oncologists to those who would definitely fall into the 'elderly' age group and therefore an age limit of 70 was decided upon rather than 65 in the design of the questions.

3.2.2 Study setting

The survey aimed to capture the views of all currently practising consultant neuro-oncologists in the UK. Consultant neuro oncologists were defined as consultants in clinical or medical oncology who regularly treat neuro oncology patients and attend local MDTs. There is no national database of neuro-oncology consultants and therefore collating the list of members was performed through examining conference attendances, The Brain Tumour Charity database and mainly via direct telephone contact with secretaries working at all of the oncology centres within the UK. E-mail addresses were collated. Participants were excluded if not currently practising due to long term illness, maternity leave or having retired.

Data were collected from November 2015 to December 2015. A link to the online survey was e-mailed to all participating consultant neuro oncologists. 1

subsequent reminder e-mail was sent. As the survey was anonymised to prevent reporting bias, it was not possible to identify the non-responders to remind them further.

3.2.3 Ethical approvals

The survey was academically supported by The Brain Tumour Charity and the NCRI Brain Tumour Clinical Studies Group but no funding was required. The survey was voluntary, anonymous, aimed only at healthcare professionals and therefore was not considered to require national ethical approval. This was discussed with the Research and Development department at the investigator's institution.

3.2.4 Questionnaire

The survey was kept purposefully short in order to increase the likelihood of a high response rate. It was divided into 3 sections and participants were encouraged to leave comments in a free text box after each question and at the end of the survey.

Referral patterns

Under-treatment of older cancer patients is well recognised[147]. One potential reason for this is a lack of referrals from primary care or MDMs to oncology outpatient clinics on the basis of age discrimination. When older patients are discussed in MDM meetings there can be a focus on chronological age. Although performance status is meant to be documented at MDM meetings, this is a crude measure of patient fitness and often more ambiguous terminology is used[148]. We were interested in how many patients over the age of 70 discussed in neuro-oncology MDMs were subsequently seen in outpatient oncology clinics in order to see if this was a potential area for improvement.

Clinical assessment of older GBM patients

There is no current standardisation of the clinical assessment of older cancer patients, especially within the neuro oncology cohort. The second section of the questionnaire concentrated on how clinicians currently assess elderly GBM patients and how importantly they rank certain clinical, pathological and radiological characteristics (see Table 3.1). Given the rise in the use of geriatric

assessments in other tumour sites, we also enquired as to whether consultants routinely perform any form of cognitive or frailty screening in clinic.

Table 3-1 Relevant factors for clinical assessments

Factor	Factor
Age 70-75	Family support network
Age 75-80	Extent of surgical resection
Age 80-85	MGMT methylation status
Performance status	Availability of clinical trials
Co-morbidities	Size of tumour and imaging features

Multidisciplinary support

When deciding on treatment for older cancer patients, a geriatric assessment can provide vital information which can be missed during a usual consultation. A comprehensive geriatric assessment involves the multidisciplinary team with input from physio and occupation therapists. For neuro oncology patients, a speech and language team are also ideally part of the assessment process. We were interested to know how many current UK clinics have these services available to them and the opinion from the clinicians on their usefulness.

3.2.5 Data collection and analysis

Data was collected and analysed using the Survey Monkey tool and Microsoft Excel 2010. Thematic qualitative analysis was performed on the free text comments.

3.3 Results

3.3.1 Response rate

93 practicing neuro oncology consultants were identified. Confirmation of correct e-mail addresses was acquired in all. There were 56 responders resulting in an overall response rate of 60%. 45 participants responded after the first link was sent, 11 further after the reminder e-mail.

3.3.2 Referral patterns

Respondents assessed on a 5 point Likert scale how many patients aged 70 or over discussed at their local multidisciplinary meeting were subsequently referred to their oncology outpatient services. All participants replied that at least some of those discussed were referred. 20% of participants saw all patients aged 70 or over (Table 3.2).

Table 3-2 Referral patterns from MDMs

	Respondents N (%)
None of them	0
Some of them	8 (14%)
About half of them	10 (18%)
Most of them	26 (46%)
All of them	11 (20%)
Skipped question	1 (2%)

3.3.3 Clinical assessments

85% of respondents valued performance status as ‘extremely important’ when assessing elderly GBM patients for treatment, a higher proportion than for any other factor. This was followed by co-morbidities then age over 80. Despite the publication of the NORDIC and NOA-08 trials showing improvement in survival and response to chemotherapy in those patients with methylation of the MGMT promoter region[39,55], there was a marked difference in how responders ranked the importance of MGMT methylation status. 6% of responders do not have MGMT status available when they are making their treatment decisions,

whereas 48% feel that MGMT status is very or extremely important. The availability of clinical trials was felt to be least important (Table 3.3).

Table 3-3 Importance of clinical parameters in assessments

Factor	Not imp	Slightly imp	Moderately imp	Very imp	Extremely imp	N/A
Age 70-75	8%	23%	40%	17%	12%	0%
Age 75-80	0%	10%	33%	38%	19%	0%
Age 80-85	0%	0%	15%	50%	35%	0%
Performance status	0%	0%	0%	15%	85%	0%
Co-morbidities	0%	4%	15%	37%	44%	0%
Family support network	0%	27%	40%	25%	8%	0%
Extent of surgical resection	2%	17%	54%	19%	8%	0%
MGMT methylation status	4%	15%	27%	29%	19%	6%
Availability of clinical trials	17%	19%	23%	21%	14%	6%
Size of tumour and imaging features	0%	12%	30%	42%	16%	0%

80% of respondents do not routinely perform a formal cognitive or frailty screening test on elderly GBM patients in clinic. 2% were unsure and of the 18% that do perform a test, the most common is the Mini-Mental State Examination. Other tests mentioned include the Montreal Cognitive Assessment and the Abbreviated Mental Test Score. Interestingly there is a lack of knowledge as to the use of cognitive or frailty screening with one respondent writing '*both these assessed as part of clinical examination'.*

Of those who did perform a cognitive or frailty screening test, 57% felt it changes the treatment decisions made at local MDT around half the time.

3.3.4 Multidisciplinary support

31% of respondents had access to one or more of physiotherapy, occupational therapy or speech and language services during outpatient clinics. A number of participants commented that they have services available to refer to but they are not physically present at the time of the initial assessment where treatment decisions are made. 70% of those who had services available at some time point in the patient journey felt that their assessment rarely changed the initial treatment decision. The lack of multidisciplinary support within the first patient clinic may explain why so few of the treatment decisions are influenced by the opinions and assessments of the multidisciplinary team.

> *'They may not be seen on the same day, but we have specialist neuro AHPs (physio, OT and SALT) who can pick them up promptly'*

> *'In second clinic (not in first new patient clinic) have two senior AHPs, one a former physio, the other a former SALT, but able to assess and support generally and refer on'*

> *'Only if I request input after clinic – they are not available during my clinic'*

> *'We have in MDT so can refer but they are not present in clinic'*

3.3.5 Additional comments

A theme that emerged from the additional comments participants left at the end of the survey was the importance of a proper assessment prior to the MDM discussion.

> *'Performance status is v important and is poorly communicated by referrers to MDM. Using a frailty or cognitive test result as an essential part of the referral might improve selection of patients'*

> *'Assessing how intensive to be is very difficult. Increasing numbers in view of the ageing population. Most importance for us is the threshold for surgery'*

Many geriatric assessments are performed within the oncology clinic after the initial MDM discussion. It is interesting to note that the timing of these might be

better served if placed earlier on in the patient journey. A few centres already have this in place and others are looking to develop this process.

> *'Physio/OT etc is assessed prior to oncology appt'*
>
> *'Our MDT is sensible and recommendations defer to clinical assessment'*
>
> *'As part of extended network neurosciences MDT, we are in the process of developing local supports'*
>
> *'But looking at* [developing] *this model'*

Another theme which emerged was the importance of the clinical nurse specialist (CNS) in the assessment process.

> *'Input from specialist nurses who have dealt with the patient on the ward and who are present as key workers in new patient clinic is also very helpful'*
>
> *'The clinical nurse specialists also have a big say in whether to offer treatment'*

In many centres the CNS is the mainstay of support throughout the treatment pathway for the patient and often gains insights into their fitness and wellbeing which are not revealed to the clinicians involved.

3.4 Discussion

This is the first study looking at how patients aged 70 and over with GBM are currently assessed across UK neuro oncology clinics. Compared to other tumour sites, there are a small number of practicing neuro-oncologists in the UK. Although not all of the participants responded to the survey, we believe that a response rate of 60% is adequate to draw conclusions from this cohort[149].

There is a growing need to improve outcomes whilst maintaining quality of life amongst elderly oncology patients. Chronological age alone is insufficient to predict for fitness, frailty or tolerance to treatment and under treatment is one of a number of reasons why elderly oncology patients do less well[150]. We have shown that in one fifth of the UK neuro-oncology MDMs represented in this survey, only 50% of the elderly patients with at least a radiological diagnosis of GBM discussed ever meet a neuro-oncologist.

While previous work has suggested that performance status is a blunt tool for detecting the subtle and nuanced symptoms that GBM can evoke[117], it was defined as ‘extremely important’ in determining treatment decisions by a large majority of participants in our survey. Although this is consistent with international data, the International Society of Geriatric Oncology recommended in 2015 that a geriatric screening assessment rather than performance status be performed on elderly oncology patients to assess for referral for a full geriatric assessment[75]. As displayed by this survey, in neuro oncology clinics this is yet to occur with 80% of respondents not routinely performing even a cognitive or frailty test let alone a full geriatric assessment. The reasons for this are likely multifactorial, including a lack of time and awareness[151], but a key aspect may be the lack of a standardised and well validated tool for this cohort. The need for geriatric assessment screening tools within neuro oncology was highlighted by the participants, 50% of whom who answered that a screening assessment changed their decision making half of the time.

Perhaps unsurprisingly, the survey displays the national heterogeneity in oncological services in terms of the patient pathway through the assessment and treatment system and the availability of physiotherapy, occupational

therapy and speech and language services. More interesting was the view, from those who did have access, that these assessments very rarely changed the initial management decision. This may be due to the assessments being performed too late in the patient pathway, after the initial consultation and treatment decisions have been made. It was beyond the scope of this survey to assess the potential benefit from early involvement of a multidisciplinary team however it is interesting to note that a few centres have started to develop this pathway. The use of joint surgical and oncological appointments, including the input from multidisciplinary teams, at the point of diagnosis for these patients may enable the process of 'prehabilitation' or improving patient fitness prior to treatment to become possible. This would fit with a comprehensive geriatric assessment model as discussed earlier in this thesis.

Limitations of this study include response bias as those who are interested in geriatric oncology may have been more likely to participate. As it was anonymous it was not possible to explore further any individual or geographical distribution to the response rate. We aimed to include all UK based consultant neuro oncologists however this is a relatively small sample within the context of the international population and results may not be transferrable to different nations.

Despite a handful of recent trials focusing on elderly GBM patients, management of this cohort continues to prove challenging. Previous reports have identified multiple pre-treatment prognostic factors including molecular characteristics (notably MGMT and IDH status), comorbidities, neurological status, location of lesion, marital status, language deficit and radiological features. Few of these trials were designed specifically for the older cohort of patients. Treatment initiation decisions within this cohort are therefore still highly subjective.

There remains an urgent need to develop and validate a customized neuro-oncology based assessment tool for this vulnerable patient group and to determine its prognostic and predictive value in a prospective study. Such a tool could incorporate components of the geriatric assessment alongside

pathological and radiological markers. As respondents from our survey commented, *'treatment has to be very individualised in glioma patients and cognitive impairment, frailty and informed patient choice are the most important factors.'*

Chapter 4 Geriatric assessment for OLDEr patients with Glioblastoma within Neuro-oncology clinics (GOLDEN study)

4.1 Introduction

Our global population is ageing and with it are our oncological patients. By 2030 it is predicted that almost 70% of cancer patients will be aged 70 or over[3]. Within general oncology the interest in using geriatric assessments to help guide patient optimisation and treatment decisions is flourishing however there is a dearth of such studies in the neuro-oncology setting. A geriatric assessment involves multiple domains including socioeconomic factors, functional status, cognition and psychological health. These are vitally important within the neuro-oncology patient population as the unique placement of their tumour can have direct effects on their ability to maintain their health during diagnosis and treatment.

Treatment for older GBM patients is based around prolonging and maintaining quality of life. Primary outcomes from traditional randomised controlled trials tend to concentrate on overall or progression free survival however it is vital to focus on quality of life and maintaining functional status for the short time that these patients have. This is reflected in the 2018 consensus paper from the International Society of Geriatric Oncology who state that age does have an impact on treatment decision making and that *'older patients are often more vulnerable to treatment toxicities, which increases the relevance and value of quality of life'*[15].

The use of geriatric assessment has shown to predict morbidity and mortality from cancer in other tumour types. There is a lack of awareness of geriatric assessments within the neuro-oncology setting and, where knowledge is present, there is an assumption that the process is too time or resource draining to be feasible. Our aim as neuro-oncologists should be to offer the patient the best treatment on the basis of their individual preferences and functional ability and the geriatric assessment is vital in this process. As yet, the geriatric assessment process has not been validated within the neuro oncology setting

and ultimately clinical trial designs in this cohort should include a neurologically focussed assessment. In order to make this a viable prospect within an overstretched and underfunded NHS, it is first necessary to see whether one can perform a geriatric assessment within the confines of a standard NHS outpatient clinic without extra staff. If so, then the next step is a study powered to assess how the results of this geriatric assessment can be used to guide management and treatment decisions in this patient cohort.

I here present the results of the GOLDEN study; a feasibility study, conducted across three UK based cancer centres, looking at embedding a modified geriatric assessment within the neuro-oncology NHS outpatient clinic. Part of this study involved a small pilot examining whether pre-treatment MRI scans can be used to predict for toxicity and survival from cranial radiotherapy, this will be discussed in a later chapter.

4.2 Chapter overview

The GOLDEN study was designed primarily as a feasibility study however the study also involved a qualitative research section with interviews with the staff involved in running the study. This chapter aims to outline the methods and results of main study in Part A followed by the qualitative sub study in Part B.

Part A – Feasibility study

4A.1 Methods

4A.1.1 Study design

A prospective, multicentre feasibility study, aimed at assessing whether it is achievable to embed a neuro-oncology focussed geriatric assessment within the NHS neuro-oncology outpatient setting. The primary outcome measure for this feasibility study was recruitment rate. This was decided upon as an objective measure to reflect the viability of delivering a geriatric assessment in this setting.

4A.1.2 Statistical consideration

Sample size

As this was a feasibility study, a formal sample size calculation was not performed as the results of the study can be used to generate a confidence interval for sample size calculations for future larger studies in this population. Retrospective work performed by the researcher[88] has shown that around 50 patients per year across the three sites meet the eligibility criteria. The sample size was therefore set at 50 as this was felt to be an achievable target within the time allowed as well as giving sufficient data for analysis.

Statistical analysis

Data was collated in Microsoft Excel and analysed using SPSS. All questionnaires were scored using validated scoring systems as described by the authors of the questionnaires and relevant published articles as referenced. Baseline demographic and questionnaire data on all participants was summarised and presented using descriptive statistics, presenting means with standard deviation for normally distributed variables, median with interquartile

range for skewed continuous variables and proportions with percentages for categorical data.

The primary outcome measure of interest was expressed using descriptive statistics. Secondary outcomes measures were examined using SPSS. Univariable analysis was performed with Kaplan-Meier plots and log rank testing used to investigate for relationships with survival. Cox regression models were performed to assess for effect size and to check the proportional hazard assumption was met. Multivariate analysis cox regression models were tested using those parameters which were significant in univariable analysis; these results have been interpreted with caution as this is a feasibility study, not designed or powered to provide information apart from on the primary outcome measure.

The feedback from participants gathered from the questionnaires were analysed descriptively using Likert scales as outlined below.

4A.1.3 Ethical regulations

Ethical approval was granted from the West Midlands – Solihul Research Ethics Committee, reference number 16/WM/0408. The Health Research Authority approval was granted and local research and development agreement in place in all three sites before the study opened. The study was sponsored by Brighton and Sussex University NHS Trust and adhered to Good Clinical Practice research guidelines[152].

A substantial amendment was made to the protocol after the study opened which was approved by the West Midlands – Solihul Research Ethics Committee, the Health Research Authority and all three local research and development offices. Initially the study involved a paper questionnaire to be answered by the nurses involved in recruiting to the study and performing the assessments. This was changed to allow the Chief Investigator to perform semi structured interviews with the nurses in order to gain a deeper insight into the acceptability of the study. The amendment did not affect the participants and therefore they did not require reconsenting.

4A.1.4 Study setting

Participants were identified from patient lists during weekly multidisciplinary meetings (MDMs) involving neurosurgeons, neuro-oncologists, clinical nurse specialists, research nurses and allied health professionals across 3 NHS sites. These were: Brighton and Sussex University Hospitals NHS Trust in Brighton, The Royal Marsden NHS Trust in Sutton and The Beatson West of Scotland Cancer Centre in Glasgow. Participants were approached and recruited either as inpatients in one of these NHS trusts, or when they attended for an outpatient neuro-oncology clinic appointment.

Further details on ethical approval, the amendment process and the PIS can be found in Appendix 1.

4A.1.5 Study population and recruitment

Eligible patients were those aged 65 years or over with a new diagnosis of GBM who had been referred to the neuro-oncology outpatient clinic in the three centres where the study was open. Patients had been diagnosed with a GBM either via histological confirmation following biopsy or debulking of their tumour or by radiological confirmation from a consultant neuroradiologist in the MDM setting. Most clinical trials involving patients with GBM include only those with a histological diagnosis. In a real world scenario, a number of older patients are seen in neuro oncology clinics with a radiological rather than a histological diagnosis and treated on this basis. Our aim in this study was to capture a realistic representation of the older UK GBM population and thus we included those with a radiological as well as histological diagnosis. A multi-centre approach was used to increase recruitment numbers given the rare nature of this disease, to provide demographic heterogeneity and to test the feasibility of the geriatric assessment process in more than one NHS facility.

Eligible participants were identified from MDM meetings by the local trial and clinical team. The researcher was not involved in identifying participants, thus decreasing the exposure to identifiable patient details. Eligible participants were recruited in a consecutive manner in each centre over the 14 month study period.

4A.1.6 Eligibility Criteria

Inclusion criteria

- Adult patients 65 years or older
- Diagnosis of GBM from histopathological verification at time of surgery or radiological confirmation by a consultant neuro radiologist within an MDM setting
- Well enough to attend an outpatient neuro oncology clinic
- Referred to one of the trial centres for their neuro oncology assessment and/or treatment

Exclusion criteria

- Patients with uncertain histological or radiological diagnosis
- Patients unable to complete the questionnaires even with the help of a carer/member of trial team
- Patients lacking capacity

4A.1.7 Screening

Potentially eligible participants who had been identified from the MDM were screened by a member of the clinical or trial team either as an inpatient after they had been informed of their diagnosis, or at their first outpatient neuro oncology clinic. It was necessary that patients were aware of their diagnosis prior to being approached for the study due to the information on the PIS. Each participant was given a patient information sheet (PIS) and adequate time to read and understand what was involved in the study, including the chance to discuss it with a member of the study team before signing a consent form. The consent form was signed at the baseline visit prior to commencing the study. The participant's GP was made aware that the participant was enrolled on this study via a standardised GP letter that was sent by the trial team after the participant was recruited. The participant was aware and consented to this being done. If the participant had received the PIS whilst an inpatient, they had time to take it home with them and then give consent when they came for their first neuro oncology outpatient visit. If the participant was given the PIS at that first outpatient visit they could consent the same day if they and the trial team were happy they understood the premise of the study or they could consent at their next visit if they were returning to a neuro oncology outpatient clinic

appointment prior to starting any treatment. No extra clinic visits were required for the study.

4A.1.7 Study visits

Baseline visit

Once consent was received, study activities were undertaken as per the study protocol. Participants were assigned a study number, the case report form (CRF) was completed to document demographic, medical, pharmacological, social and treatment details. Questionnaires were completed by the participant, including two self-administered questionnaires and three performed by the study team with the participant. The participant was then given a questionnaire to answer about their experience of taking part in the study. Participants took this questionnaire home with them with a stamped addressed envelope and were asked to post it back or to bring it to their next clinic visit. The clinical nurse specialist (CNS) or member of the study team could telephone the patient to remind them to do this, or complete it with the patient over the phone if the patient was willing to do this.

Follow up visits

Participants attended follow up visits as per the usual schedule within their NHS trust. No extra visits were required for the study. At follow visits, ongoing participation in the study was confirmed and a toxicity assessment CRF completed by the clinician or member of the study team reviewing the patient. No further questionnaires were required. Please see Appendix 2 for an example of the CRF.

4A.1.8 Geriatric assessment

A modified geriatric assessment tool was developed by the researcher specifically for this study. This covered the domains suggested by the EORTC minimal dataset[74] (as described earlier in this thesis) and used previously validated questionnaires. These comprised of the Lawton and Brody Instrumental Activities of Daily Living (IADLs), the Hospital Anxiety and Depression Scale (HADS), the G8 screening questionnaire (G8), the Montreal Cognitive Assessment tool (MoCA), the Trail Making Test B (TMTB), ECOG

performance status and the Charlson Comorbidity Index (CCI). The study proforma included sections for the patient date of birth, gender, social status, mobility, medication list, details of tumour location and focality and treatment received.

IADLs

The Lawton and Brody Instrumental Activities of Daily Living[153] is a self-reported questionnaire that aims to assess the ability of an older person to live independently in the community. Designed in 1969, it has been extensively used within the oncological community. Although there are a number of different screening tools that can be used for assessing current functional ability in daily tasks, the EORTC minimal dataset advises the use of IADLs and thus the researcher chose this questionnaire[74]. As discussed in the literature review earlier in this thesis, the recent ASCO recommendations have also supported the use of IADLs as a valid screening tool to assess for functional disability[13].

The IADLs questionnaire is designed to assess current level of function and focusses on eight realms of ability, outlined in Table 4.1. Each domain is scored from 0 to 1. The total scores range from 0 (low function, dependent) to 8 (high function, independent). Scores below the maximal level of 8 indicate impairment in daily functional abilities.

Table 4-1 Instrumental Activities of Daily Living domains

Domain	
1. Ability to use telephone	5. Laundry
2. Shopping	6. Mode of transportation
3. Food preparation	7. Responsibility for own medications
4. Housekeeping	8. Ability to handle finances

HADS

The Hospital Anxiety and Depression Scale (HADS) is a widely used well validated tool to assess for anxiety and depression. Although initially designed to be used for general hospital outpatients where it has shown to accurately predict for states of depression and anxiety[154], it has been used extensively

amongst the oncological cohort in an inpatient and outpatient setting[155]. Although there are a number of different depression screening tools available (ASCO recently recommended the Geriatric Depression Scale as the standard tool) there is evidence to suggest that HADS has been the most widely used amongst glioma patients so far[112].

Participants self-complete 14 statements, 7 related to symptoms of anxiety and 7 to symptoms of depression, see Table 4.2. Each statement has a Likert response scale of 4 optional answers. These are scored from 0-3 with an overall maximum score of 21 for each of anxiety or depression. Scores of 0-7 are classified as normal, scores of 8-10 as borderline abnormal and scores of 10-21 as abnormal.

Table 4-2 Hospital Anxiety and Depression Scale

Depression	Anxiety
1. I feel as if I am slowed down	1. I feel tense or wound up
2. I still enjoy the things I used to	2. I get a sort of frightened feeling like 'butterflies' in the stomach
3. I can enjoy a good book or radio or TV programme	3. I get a sort of frightened feeling as if something awful is going to happen
4. I can laugh and see the funny side of things	4. I feel restless as if I have to be on the move
5. I look forward with enjoyment to things	5. Worrying thoughts go through my mine
6. I feel cheerful	6. I get sudden feelings of panic
7. I have lost interest in my appearance	7. I can sit at ease and feel relaxed

G8 questionnaire

The geriatric eight questions (G8) screening tool was first developed in the multicentre ONCODAGE study by Soubeyran in 2011 as a screening method to assess which patients may benefit from a full CGA. It has been validated against a full CGA[93] and more recently used in a retrospective study specifically looking at older GBM patients[97]. It was included in this study's geriatric assessment toolkit as it makes up part of the EORTC Elderly 'minimal dataset'

as discussed earlier in this thesis. The G8 is usually administered by a member of clinical or research staff.

The G8 covers a question on age and then 7 questions taken from the Mini Nutritional Assessment, see Table 4.3. It is traditionally scored from 0-17 with a cut off of 14 used to indicate an abnormal result. However a recent study has suggested that using 2 cuts offs, at 10.5 and 14.5 to produce 3 groups of differing risk, may be suitable in GBM patients[97].

Table 4-3 G8 questionnaire

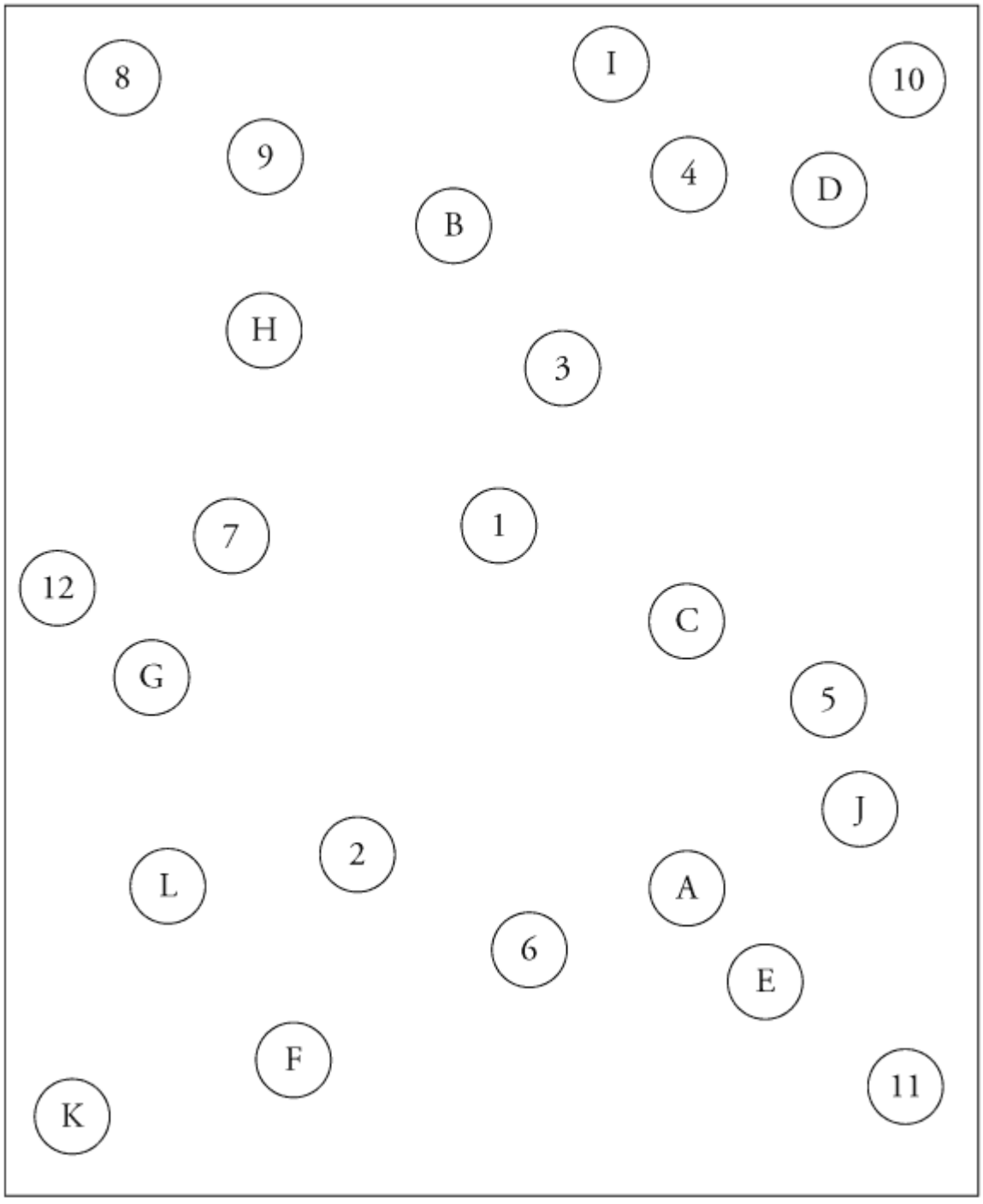
Items	Possible answers
1. Has food intake declined over the last 3 months due to loss of appetite, digestive problems, chewing or swallowing problems?	0: severe decrease in food intake 1: moderate decrease in food intake 2: no decrease in food intake
2. Weight loss during last 3 months	0: weight loss > 3kg 1: does not know 2: weight loss between 1 and 3 kg 3: no weight loss
3. Mobility	0: bed or chair bound 1: able to get out of bed/chair but does not go out 2: goes out
4. Neuropsychological problems	0: severe dementia or depression 1: mild dementia or depression 2: no psychological problems
5. Body Mass Index	0: BMI < 19 1: BMI = 19 to < 21 2: BMI = 21 to < 23 3: BMI $\geq$ 23
6. Takes more than 3 medications a day	0: yes 1: no
7. In comparison with other people of the same age, how does this person consider his/her health status?	0: not as good 0.5: does not know 1: as good 2: better
8. Age	0: > 85 1: 80-85 2: < 80

Trail Making Test B

The Trail Making Test (TMT) is a neuropsychological test which can be used to measure a number of cognitive domains including visual-motor skills, sequencing, mental flexibility and processing speed[156]. The most common variant of the test involves two sections, TMT Part A (TMTA) and TMT Part B (TMTB). The test is timed; the participant uses a pencil to connect 25 randomly distributed encircled targets on a sheet of paper. In Part A the targets are all numbers (1 – 2 – 3 – 4 – etc) and the participant has to connect them in sequential order. In Part B they are alternating numbers and letters (1 – A – 2 – B – 3 – C – etc), see Figure 6. If the participant makes an error then the person administering the test corrects them before they move on. As the test is timed the rate of errors are mirrored in the overall time taken to perform the test. A cut off of 300 seconds is well recognised[157] and was used in this study.

Many neurocognitive tests require comprehensive and extensive training however the TMT is accessible and can be performed simply by members of clinic staff. In this study it was felt that a neuro-oncology focussed GA should have a greater emphasis on cognition than is outlined in the EORTC minimal dataset but that performing both TMTA and TMTB would be too time consuming for the participants. A modified TMTB is incorporated in to the Montreal Cognitive Assessment Tool (MoCA) as outlined below. However, as described earlier, there is evidence to show in younger GBM patients the full TMTB can correlate with overall and progression free survival[115,116] and thus the researcher included a full TMTB alongside the MoCA in this study.

Figure 6 Trail Making Test B



MoCA

The Montreal Cognitive Assessment (MoCA) is a widely used screening tool to detect for cognitive impairment. It is a 1 page document which is open access and already used in some oncology centres as routine screening for older GBM patients[158]. It has been validated against the MMSE, and shows sensitivity of 90% and specificity of 87% in detecting mild cognitive impairment[159].

It covers several cognitive domains; short term memory recall by learning 5 nouns with delayed recall after around 5 minutes (5 points); visuospatial processing using clock drawing (3 points) and copying a three-dimensional cube (1 point); executive functioning using an adapted TMTB (1 point) a phonemic fluency task (1 point) and a two item verbal abstraction task (2 points). Attention, concentration, and working memory were tested using a sustained attention task (finger tapping; 1 point), subtraction of serial-7s (3 points), and repeating digits forward and backward (1 point each). Language assessment occurs via naming of three low-familiarity animals (lion, camel, rhinoceros) (3 points), repetition of two complex sentences (2 points), as well as the previous fluency task; and lastly orientation to time and place (6 points). The score is adapted by the addition of 1 point for education levels of 12 years or less, making the maximum score achievable of 30. A score of 26 or over is used as the cut off for normal. See the CRF in Appendix 2 for an example of the MoCA questionnaire.

4A.1.9 Clinical details

Clinical details ascertained by review of medical notes during the consultation were: date of diagnosis (defined as the MDM date at which the histology from their surgery for GBM was confirmed or, if not receiving surgery, then a scan was confirmed as GBM by a consultant neuroradiologist), surgery performed (none, biopsy, subtotal resection or total resection (>90% tumour removed as confirmed at MDM discussion) and ECOG performance status.

Clinical details ascertained by direct questioning during the consultation were: date of birth, gender, past and present comorbidities, current medications including steroid use and dosage, social situation (lives alone, with partner, with

family, with friend, presence of care package, other) and mobility (independent, walks with 1 stick, walks with 2 stick, need frame, wheelchair bound, other).

The social situation is vital for any geriatric assessment. It was included partly to reflect the requirements of the EORTC minimal dataset and also because a large SEER database study in 2005 showed a significant association in younger GBM patients between being married and improved overall survival[91].

CCI

The Charlson Comorbidity Index[83] is part of the EORTC minimal dataset and is thus recommended for any clinical trial involving older patients. It is a validated scoring system for classifying comorbidities with a maximum score of 37, see Table 4.4. In oncological patients the score for cancer is not given for their primary disease. The CCI score was calculated by the clinical nurse specialist from the comorbidity history provided by the participant from direct questioning.

Table 4-4 Charlson Comorbidity Index

Comorbidity	Points		Points
Myocardial infarction	1	Diabetes Mellitus (with end-organ damage)	2
Congestive cardiac failure	1	Hemiplegia	2
Peripheral vascular disease	1	Moderate / Severe chronic renal failure	2
Cerebrovascular disease (except hemiplegia)	1	Second malignancy (non metastatic)	2
Dementia	1	Leukaemia	2
Chronic obstructive pulmonary disease	1	Lymphoma	2
Connective tissue disease	1	Moderate / Severe liver disease	2
Ulcers	1	AIDS	2
Mild liver disease	1	Second malignancy (metastatic)	2
Diabetes Mellitus (without end-organ damage)	1		

4A.1.10 Pathology

As is now standard practice, those patients who underwent surgery had histopathological analysis performed on their tumour samples. In the 3 centres in this study, it is routine to test for IDH1 status in order to further categorise tumours as per the new WHO classification[18] and to look for MGMT promoter methylation which has been used as a prognostic and predictive biomarker in GBMs. Patients gave consent for their medical notes to be examined for the study purposes and thus the details of their IDH1 and MGMT status were obtained. The pathological reviews were done within the local centres as per the usual NHS process.

4A.1.11 Toxicity assessments

Toxicity assessments were performed on those patients who underwent chemotherapy, radiotherapy or both. They were measured using the Common Terminology Criteria for Adverse Events v0.4 (CTCAE v0.4)[160]. The study was designed not to involve any extra hospital visits for the participants and so toxicity criteria were collected at each patient follow up visit according to the usual clinical follow up schedule in each site. This was continued for 3 months of follow up after the end of treatment to reflect the timeframe for acute toxicities from radiotherapy or chemotherapy.

4A.1.12 Feedback from participants

After enrolment in the GOLDEN study and completion of the assessments by the participants, they were asked to self-complete a 6 point questionnaire followed by an open box for comments, see Table 4.5. This was scored using a 5 point Likert scale. This was done immediately after the GOLDEN study assessments during their first outpatient appointment or taken home by the patient, completed at a later date and returned at a subsequent outpatient visit.

Table 4-5 Participant feedback template

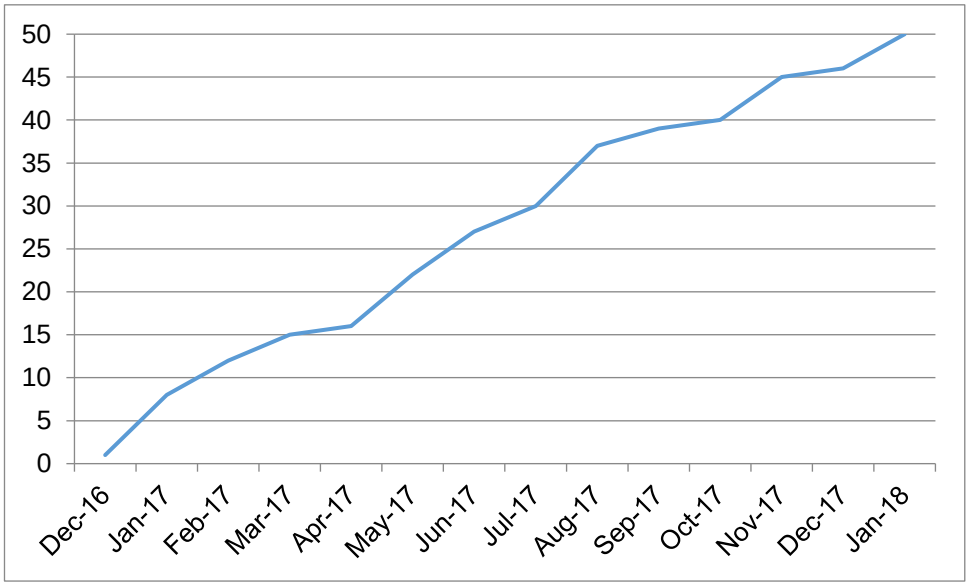
	Disagree	Partly agree	Neutral	Mainly agree	Totally agree
I was given enough time to read the patient information sheet and consent form and have my questions answered if necessary					
I was treated with respect throughout the study period					
I had enough time to complete the questionnaires comfortably					
I found completing the questionnaires distressing					
I found completing the questionnaires tiring					
I would take part in another questionnaire based clinical trial such as this one					

4A.2 Results

4A.2.1 Recruitment rate

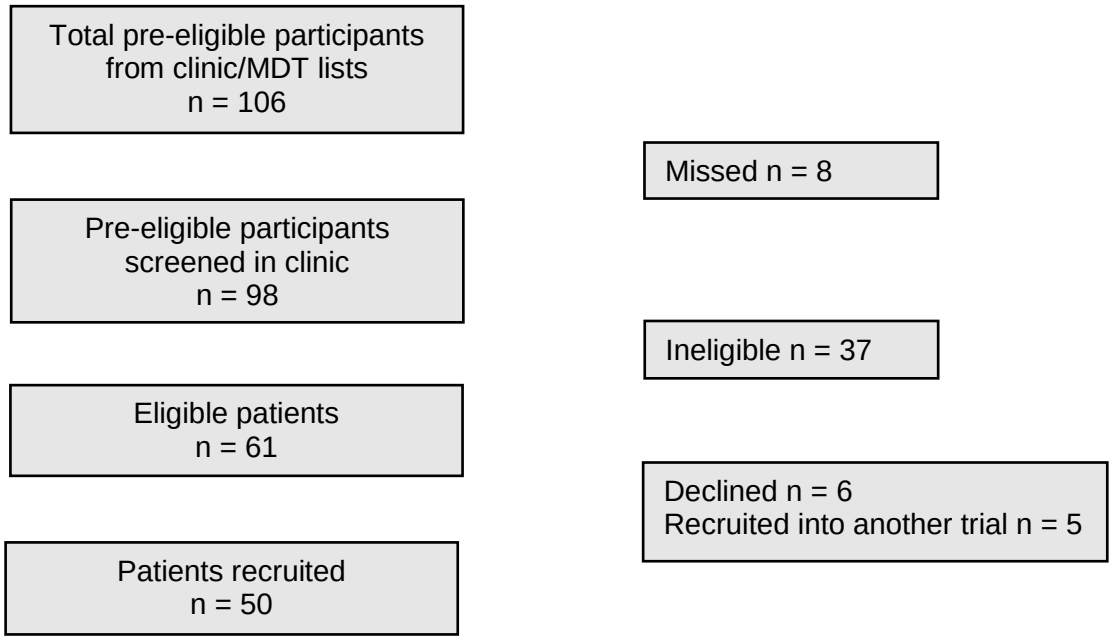
50 patients were recruited from 3 centres from November 2016 to January 2018. The recruitment rate was steady throughout the study period, see Figure 7. 3 month acute toxicity data was collected and the study closed in May 2018 at which point censoring occurred. A roughly even geographical spread occurred in the recruitment process with 20 (40%) patients recruited from The Sussex Cancer Centre (SCC), 15 (30%) patients from the Royal Marsden NHS Trust (RMH) and 15 (30%) patients from The Beatson West of Scotland Cancer Centre (BWoSCC). A target recruitment rate had been set at 80% based on previous literature.

Figure 7 Recruitment rate over time



Recruitment rate was ascertained by analysing clinic and MDT lists from each centre from the period of November 2016 to January 2018 and examining all those who met the eligibility criteria. These were then compared to the individual screening log at each centre and those patients who were screened but did not meet eligibility criteria were removed from the total number, see Figure 8. Recruitment rate was then calculated from the total number of patients who were eligible after screening.

Figure 8 Recruitment flowchart



As it was not possible to tell whether the patients who were missed from screening would have been eligible, recruitment rate was calculated by dividing the number recruited by the total number of eligible patients, resulting in an overall recruitment rate of 82% (95% CI 70%-91%).

4A.2.2 Demographics

50 patients were recruited in total. Table 4.6 shows baseline demographic and treatment data for the full cohort. The median age of the cohort was 69 years, with a range from 65 to 86. 56% of the cohort were male, in common with published literature which suggests GBMs are slightly more common in men than women[161]. The median ECOG performance status was 1 (IQR 1-2) however 8% of patients were ECOG PS 3 which suggests that performance status alone was not a factor in determining fitness for recruitment into the study. In line with published data, there was no significant predisposition for GBMS to develop in the left or right hemisphere[162].

Surgery was defined as none, biopsy, subtotal resection (STR) (<90% resected) or gross total resection (GTR) (>90% tumour resected) as confirmed by post-

operative MRI scans reviewed at the MDM. Of the 41 patients who underwent surgery, the majority (41%) had a GTR. In terms of active oncological treatment, the largest group of patients received radical treatment with 60Gy in 30 fractions of radiotherapy with concurrent and adjuvant temozolomide (TMZ) as per the Stupp protocol[38]. Of those who underwent surgery, 6 patients subsequently had no further active treatment due to a worsening of their overall status. Of the 9 patients who did not undergo surgery, 6 of them continued to receive oncological treatment in the form of 30Gy in 6# of radiotherapy alone (3 patients), 40Gy in 15# of radiotherapy alone (2 patients) and concurrent chemo radiotherapy with 60Gy in 30# and TMZ (1 patient).

Of the 36 participants who received radiotherapy, 34 (94%) completed the prescribed course. I participant was changed from 40Gy in 15# to 25Gy in 5# after 2# due to clinical deterioration. 1 participant stopped radiotherapy altogether after 5# of 40Gy/15# due to worsening clinical status. Of the 5 participants who received CRT with 40.05Gy/15#, all participants completed the concurrent TMZ course, however only 1 participant received adjuvant TMZ. The rest either had unmethylated MGMT promoter regions or had deteriorated clinically during their CRT and were not fit for further chemotherapy. Of the 14 who received radical CRT with 60Gy/30#, 13 (93%) completed the concurrent TMZ course, 1 participant had to stop due to thrombocytopenia. 11 started on adjuvant TMZ however only 6 completed a 6 month course. 3 stopped due to poor clinical status and 2 due to thrombocytopenia.

8 patients received second line treatment after progression; 1 had redo debulking surgery followed by PCV chemotherapy, 5 had PCV alone (2 with vincristine omitted). 2 patients received second line TMZ after progression having had single agent radiotherapy initially.

Median overall survival (OS) was 9.5 months (95% CI 5.0-14.0 months) in all groups. 3 month survival was 85%; 6 month survival was 63%, dropping to 43% at 12 months. Median OS in those receiving BSC was 4.3 months which is slightly higher but still in line with the national average[7]. Of those who received palliative radiotherapy alone, median OS was 6 months for those who received

30Gy in 6 fractions and 10.7 months for those receiving 40Gy in 15 fractions which may reflect both an improved outcome from higher doses of radiotherapy, and patient selection bias for treatment. This is again slightly better than results in published literature including the radiotherapy alone arm of the 2018 CCTG CE.6/EORTC 26062 trial[7,56]. In this trial, 68.3% of patients had surgical resection compared to biopsy alone. In the GOLDEN study, 45.4% of those receiving 40Gy in15# radiotherapy alone had resection performed so the improved OS is not explained by a greater degree of surgical debulking. Median survival in the temozolomide alone arm was 2.4 months which is considerably lower than published data however there were small numbers of participants within this group[39,55]. Median survival was not yet reached in either of the chemo-radiotherapy treatment arms.

Table 4-6 Baseline demographic and treatment data

Variable		**N (%) [a]**
Age [b]		69 (IQR 67.0-74.25)
Age Range		65-86
Age group:	65-69.9	27 (54)
	70-74.9	11 (22)
	75-79.9	10 (20)
	≥ 80	2 (4)
Gender:	Male	28 (56)
	Female	22 (44)
ECOG performance status [b]		1 (IQR 1-2)
ECOG performance status:	0	6 (12)
	1	28 (56)
	2	11 (22)
	3	4 (8)
	Not recorded	1 (2)
Tumour hemisphere:	Right	21 (42)
	Left	25 (50)
	Bilateral	4 (8)
Tumour focality:	Unifocal	42 (84)
	Multifocal	8 (16)

Variable		N (%) [a]
Surgery:	None	9 (18)
	Biopsy	14 (28)
	STR	10 (20)
	GTR	17 (34)
IDH1 status:	Wildtype	38 (93)
	Mutated	0 (0)
	Testing failed	3 (7)
MGMT promoter: status	Methylated	11 (27%)
	Unmethylated	24 (58%)
	Testing failed	6 (15%)
First line treatment:	Best supportive care	9 (18)
	RT (30Gy/6#)	6 (12)
	RT (40.05Gy/15#)	11 (22)
	CRT (40.05Gy/15#)	5 (10)
	CRT (60Gy/30#)	14 (28)
	TMZ alone	5 (10)
[a] unless stated	[b] median (IQR)	

4A.2.3 Data completeness

In order to assess the feasibility of the study, a surrogate secondary endpoint of data completion was used. This was set at 80%. Data completeness was measured per questionnaire and per participant in order to analyse whether there were concerns with certain questionnaires or whether it was the individual functional ability of the participant that determined completeness, see Tables 4.7 and 4.8.

All of the GA questionnaires in the study were completed at a rate of over 80% apart from TMTB (70%). There were minor geographical differences noted in the completion rates however all sites had rates over 80% for all questionnaires apart from TMTB where completion rate was 50% at SCC compared to 73% at RMH and 93% at BWoSCC. Nurses reported very differing views in how difficult they found the TMTB to administer and how useful they thought the results

were, this is explored in more detail in the qualitative analysis later in the chapter. 90% of participants completed at least 8 of the 9 questionnaires, with 54% of participants completing all of them. Again there was some geographical differences; in SCC 40% of patients completed all questionnaires, compared to 67% at RMH and 60% at BWoSCC.

Table 4-7 Data completeness per questionnaire

GA questionnaire completed	N (%)
1. IADLS	47 (94)
2. HADS	48 (96)
3. G8	50 (100)
4. TMTB	35 (70)
5. MoCA	48 (96)
6. CCI	44 (88)
7. Medication list	46 (92)
8. Social situation	50 (100)
9. Mobility	50 (100)

Table 4-8 Data completeness per participant

Number of GA questionnaires completed	N (%)
9	27 (54)
8	18 (36)
7	2 (4)
6	2 (4)
5	1 (2)
<5	0 (0)

4A.2.4 Geriatric assessment

Based on the scoring systems validated in the published literature surrounding each geriatric assessment questionnaire, the parameters of the study cohort are displayed in Table 4.9. The number of medications patients were currently taking was collected both as part of the G8 questionnaire and separately. This was felt necessary as the G8 has a cut off of 3 or more medications however 49 participants (98% of this patient cohort) were taking dexamethasone and a proton pump inhibitor when they were assessed in clinic. Data was therefore also collected on whether they were on 3 or more medications *excluding dexamethasone and PPI*. The G8 scoring system was divided both into normal/abnormal and then into 3 risk groups as discussed in the methods section.

Table 4-9 Baseline parameters of geriatric assessment

Variable		**N (%)** [a]
IADLS	Normal (8)	13 (26)
	Impaired (<8)	27 (74)
HADS		
HADS-Anxiety	Normal (0-7)	37 (74)
	Borderline (8-10)	8 (16)
	Abnormal (11-21)	4 (8)
	Not recorded	1 (2)
HADS-Depression	Normal (0-7)	35 (70)
	Borderline (8-10)	10 (20)
	Abnormal (11-21)	4 (8)
	Not recorded	1 (2)
G8[b]		15 (IQR 14-16)
G8	Normal (> 14)	29 (58)
	Abnormal (≤ 14)	21 (42)
G8	Low risk (>14.5)	30 (60)
	Medium risk (10.5-14.5)	18 (36)
	High risk (<10.5)	2 (4)

Variable		N (%) [a]
TMTB[b]		119 (IQR 63-148)
TMTB	Completed ≤ 5 mins	29 (58)
	Did not complete ≤ 5 mins	16 (12)
	Not recorded	15 (30)
MoCA[b]		25 (IQR 19-28)
MoCA	Normal (>25)	21 (42)
	Abnormal (≤ 25)	28 (56)
	Not recorded	1 (2)
CCI[b]		0 (IQR 0-1)
Medications	≤ 3 excluding dex and PPI	29 (58)
	> 3 excluding dex and PPI	21 (42)
Social situation	Lives alone	11 (22)
	Lives with partner/family	39 (78)
	Has a care package	0 (0)
Mobility	Independent	38 (76)
	Walks with 1 stick	8 (16)
	Walks with frame	2 (4)
	Wheelchair bound	2 (4)

[a] unless stated [b] median (IQR)

4A.2.5 Univariable analysis

All parameters were assessed for association with overall survival using univariate analysis. From the baseline demographics; age group, gender, MGMT methylation status, tumour laterality, focality and mass effect did not have a significant relationship with overall survival. ECOG performance status approached significance (log rank p=0.07). Cox proportional hazards assumption was met for all significant univariable parameters, these are outlined in Table 4.10.

Surgery performed was significantly associated with improved overall survival on univariable analysis with log rank testing (p=0.013). Using cox regression analysis, compared to no surgery, biopsy (HR 0.679 95% CI 0.249-1.851

p=0.450) and STR (HR 0.431 95% CI 0.133-1.395, p=0.160) were not significant. This may be due to lower participant numbers in these groups compared to GTR which decreased hazard of death by 6.4 times (HR 0.156, 95% CI 0.044-0.548 p=0.004). First line oncological treatment was again significant (overall p=0.006). Compared to no treatment, 40Gy in 15# alone (HR 0.2 95% CI 0.057-0.708 p=0.013) and radical CRT with 60gy in 30# and TMZ (HR 0.026 95% CI 0.003-0.223 p=0.001) had a significant impact whereas the other treatment regimens did not reach significance. This again is likely due to lower participant numbers in the other treatment groups.

From the neurologically focused geriatric assessment scores, an impairment in MoCA score increased hazard ratio of death by 2.7 times (95% CI 1.128-6.530 p=0.026) (See Figure 9) and impairment in IADLS increased the hazard ratio by 2.9 times (95% CI 0.983-8.541 p=0.05) (see Figure 10). Patients with impaired mobility were less likely to survive (overall p=0.033) with those using a frame 10 times more likely to have a poorer survival than those independently mobile (HR 10.7 95%CI 2.2-51.6 p=0.003). The other mobility aids were not found to be significant, this is likely to be due to small numbers in the group who presented in a wheelchair.

Figure 9 Kaplan Meier of impairment in MoCA score (cut off 26) (original in colour)

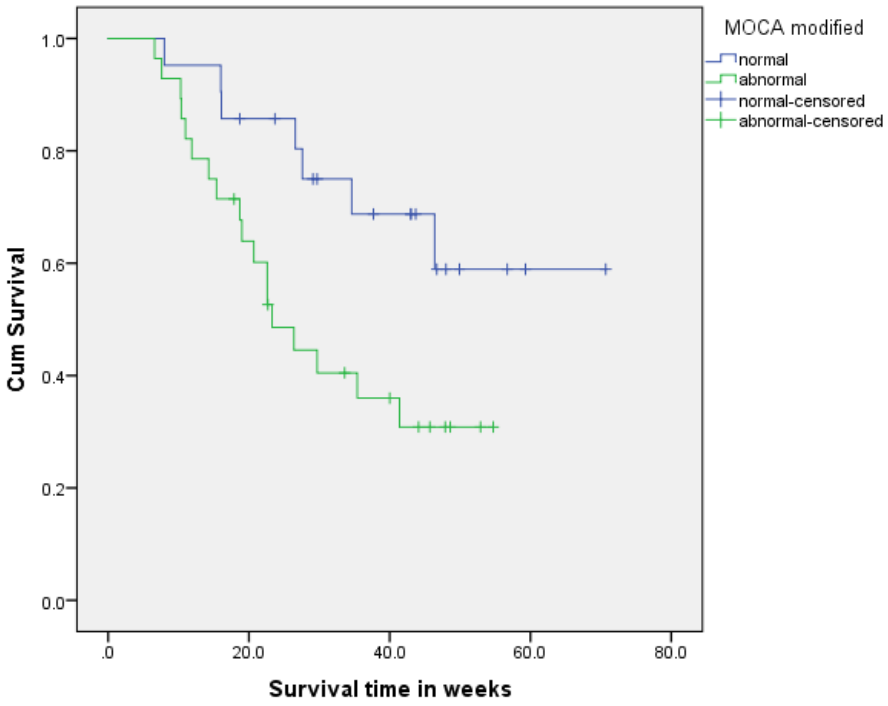
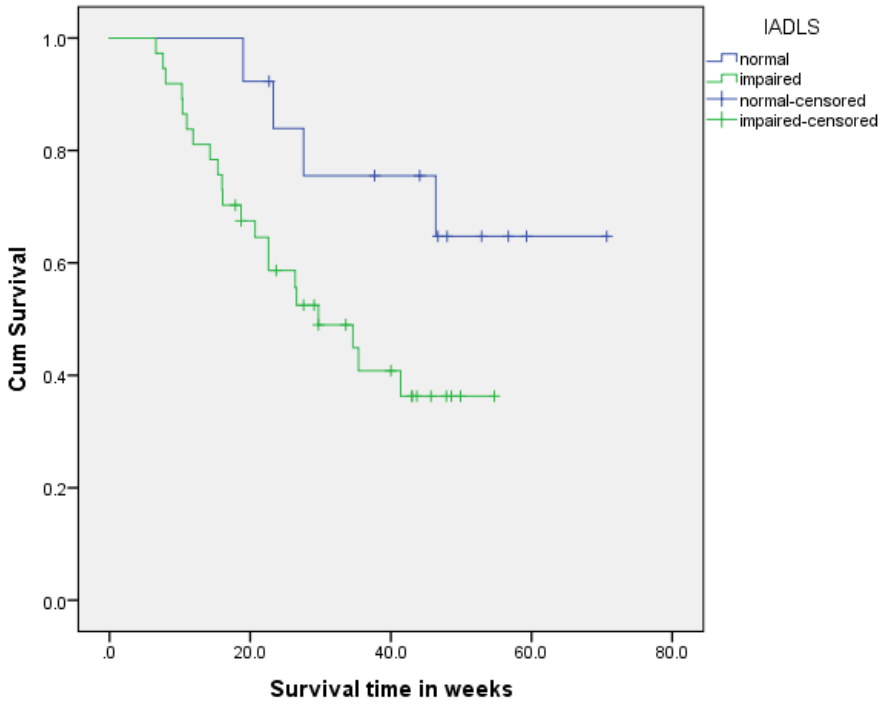


Figure 10 Kaplan Meier of impairment of IADLs (original in colour)



With the conventional G8 scoring, there was no significant difference between normal and abnormal scores however using the recently explored system of a three tier approach, it revealed that those in the intermediate scoring group had a significantly increased risk compared to those in the highest group (HR 2.38 95%CI 1.07-5.26 p=0.033) (see Figure 11). The depression score of HADS was not found to be significant however a borderline abnormal HADS anxiety score increased hazard ratio by 3 times (HR 3.1 95% CI 1.26-7.67 p=0.014) (see Figure 12). TMTB was not found to be significant, this may be due to the low numbers of participants who had it completed.

Figure 11 Kaplan Meier showing effect of abnormal G8 score (original in colour)

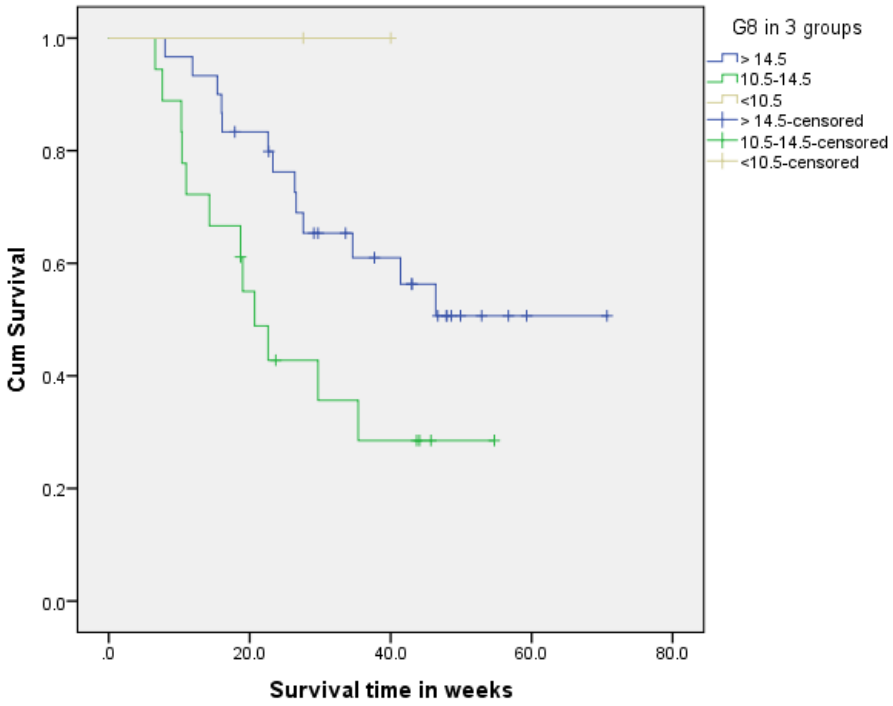


Figure 12 Kaplan Meier showing effect of abnormal HADS-A score (original in colour)

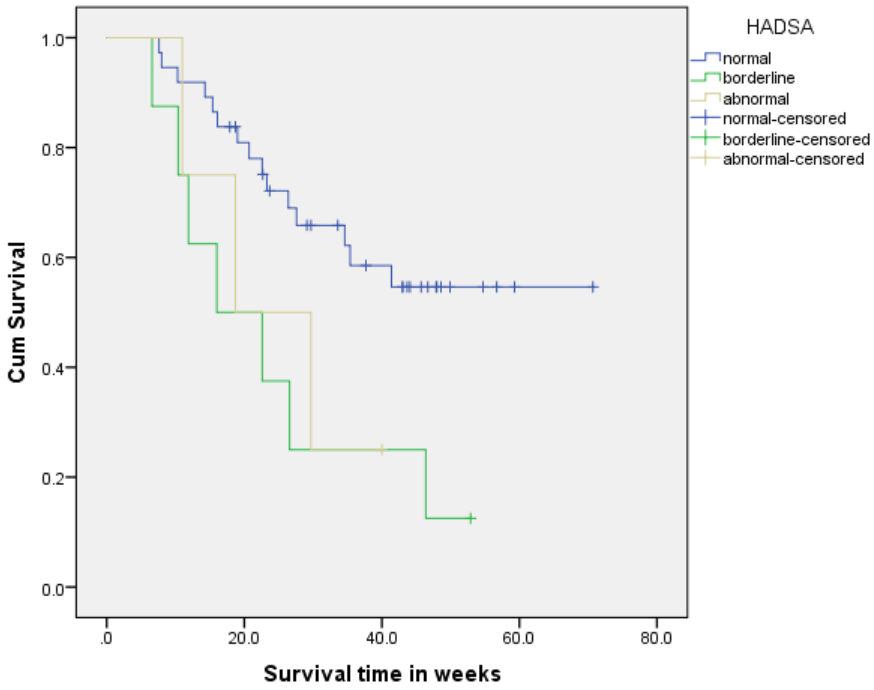


Table 4-10 Univariable analysis of overall survival

Variable		Hazard ratio	95% CI	*p*-value
Age group (compared to 65-69.9)	70-74.9	0.945	0.34-2.65	0.91
	75-79.9	1.01	0.36-2.85	0.98
	80-84.9	1.51	0.56-11.27	0.23
Gender	Female	1.22	0.56-2.68	0.62
Side (compared to right)	Left	0.59	0.26-1.34	0.20
	Bilateral	0.76	0.17-3.37	0.72
Focality	Multifocal	1.57	0.59-4.19	0.37
Mass effect	Present	0.87	0.38-2.02	0.48
MGMT promoter	Methylated	0.85	0.27-2.67	0.78
IADLS	**Impaired**	**2.90**	**1.01-8.54**	**0.05**
HADS-D	Borderline	1.51	0.59-3.89	0.39
	Abnormal	2.14	0.62-7.40	0.23
HADS-A	**Borderline**	**3.11**	**1.26-7.67**	**0.01**
	Abnormal	2.45	0.70-8.53	0.16
G8 (compared to > 14.5)	**10.5-14.5**	**2.38**	**1.07-5.26**	**0.03**
	< 10.5	0.00	Not met	0.98
TMTB	> 5 mins	0.59	0.14-2.57	0.48
MoCA	**Impaired**	**2.71**	**1.13-6.53**	**0.03**
Mobility (compared to independent)	Stick	1.17	0.39-3.46	0.78
	Frame	**10.70**	2.22-51.59	**0.00**
	Chair	1.45	0.19-11.04	0.72
Social situation	Lives with partner	0.79	0.31-2.00	0.63
Surgery (compared to none)	Biopsy	0.70	0.25-1.85	0.45
	STR	0.43	0.13-1.40	0.16
	GTR	**0.16**	**0.04-0.55**	**0.00**
Treatment (compared to BSC)	30Gy/6#	0.44	0.14-1.41	0.16
	40Gy/15# alone	**0.40**	**0.08-0.78**	**0.01**
	40Gy/15# CRT	0.33	0.05-1.18	0.10
	60Gy/30# CRT	**0.03**	**0.00-0.23**	**0.00**
	TMZ alone	0.99	0.29-3.35	0.98

4A.2.6 Multivariable analysis

Multivariable analysis was performed using cox regression models. The factors which were significant on univariable analysis were inputted into a multivariable model to provide a hazard ratio for each variable. These are outlined in Table 4.11. The factors which remained significant in the multivariable model were receiving radical treatment (HR 0.005, p=0.001), an abnormal MoCA score (HR 20.34, p=0.006) and mobility impaired by walking with a frame (HR 23.28, p=0.05). Using a chair was not significant however there were low numbers within this group which are likely to have affected results. These results must be interpreted with caution as the original study was not designed to be powered to detect significant changes and there is a risk of overfitting however the results found make clinical sense.

Table 4-11 Multivariable anaylsis for overall survival

Variable		Hazard ratio	95% CI	*p*-value
Surgery (compared to none)	Biopsy	0.51	0.08-3.32	0.48
	STR	4.74	0.33-67-.58	0.25
	GTR	0.57	0.06-5.10	0.61
Treatment (compared to BSC)	30Gy/6#	0.12	0.01-1.82	0.13
	40Gy/15# alone	0.26	0.02-3.77	0.32
	40Gy/15# CRT	0.60	0.05-7.66	0.70
	60Gy/30# CRT	**0.01**	**0.00-0.11**	**0.00**
	TMZ alone	2.07	0.13-33.95	0.71
IADLS	Impaired	1.37	0.26-7.22	0.71
HADS-A	Borderline	1.00	0.23-4.38	0.99
	Abnormal	0.26	0.01-5.43	0.38
G8 (compared to > 14.5)	10.5-14.5	0.54	0.11-2.58	0.44
	< 10.5	0.00	Not met	0.98
MoCA	**Abnormal**	**20.34**	**2.40-172.14**	**0.01**
Mobility (compared to independent)	Stick	0.65	0.11-3.81	0.64
	Frame	**23.28**	**1.07-508.75**	**0.05**
	Chair	2.20	0.17-27.89	0.54

4A.2.6 Toxicity

Toxicity data was collected during the routine NHS follow up appointments attended by the participants for up to 3 months after the end of treatment, covering the acute toxicity period. As there were no extra visits involved in the study, the time points of when toxicity data was collected differs from Trust to Trust depending on their usual follow up schedule. Some patients were too unwell to attend for follow up appointments and therefore toxicity data was not collected. If participants had not been offered oncological treatment then there was also no toxicity data collected.

Toxicity was scored using the CTCAE v4.0 classification[160]. 41 participants received active oncological treatment in the form of chemotherapy, radiotherapy or both. For patients undergoing radiotherapy, data was collected on fatigue, headache, nausea, vomiting, seizures and confusion. For those having chemotherapy, data was collected on haematological side effects, rash and constipation. Overall toxicities experienced are outlined in Table 4.12. All patients except 1 experienced grade 1-2 fatigue in at least 1 domain. 1 participant experienced grade 4 seizures. 8 participants (20%) experienced grade 3 toxicity in fatigue, confusion or haematological disturbances. The prevalence of those who had G3/4 fatigue was evenly spread across the radiotherapy treatment groups with 1 participant having 30Gy/6# of radiotherapy, 3 participants having 40.05Gy/15# radiotherapy alone, 2 having 40.05Gy/15# CRT and 1 having 60Gy/30# CRT.

Data was collected on change in steroid dose during follow up in the first 3 months. 23 (56%) participants had no change in steroid dose, 8 (20%) decreased their steroid dose and 10 (24%) increased. This is in line with published data[50].

Table 4-12 Overall toxicities

Symptom	G1/2 N (%)	G3/4 N (%)
Fatigue	36 (88)	7 (17)
Headache	8 (20)	0 (0)
Nausea	9 (22)	0 (0)
Vomiting	2 (5)	0 (0)
Seizures	4 (10)	1 (2)
Confusion	9 (22)	2 (5)
Haematological	2 (8)	2 (8)
Rash	0 (0)	0 (0)
Constipation	9 (38)	0 (0)

Part B – Qualitative analysis

4B.1 Methods

4B.1.1 Qualitative analysis

Initially the GOLDEN study was designed to have feedback from the CNSs and doctors running the study given via a questionnaire with 6 questions and an open comments box. The answers were structured around a 5 point Likert scale, see Table 4.13. The feedback was performed after the GOLDEN study had closed.

Table 4-13 Observer feedback template

	Disagree	Partly agree	Neutral	Mainly agree	Totally agree
I felt comfortable enrolling patients within this study					
The study significantly impacted on my clinic/admin time					
It was feasible to complete the assessments within the neuro oncology outpatient setting					
Completing the assessments added stress to the consultation					
Completing the assessments enhanced my relationship with the patient					
If the evidence revealed a benefit, I would be happy to incorporate the assessments from the study into my routine clinical practice with my current resources					

However, having had informal feedback during the course of the study recruitment period from the CNSs, the researcher decided to do a protocol amendment in order to enable them to perform in depth interviews with the CNSs at the end of the study period. The doctors were felt to be less involved in the day to day running of the study and so continued to be assessed by the paper questionnaires. Qualitative analysis was then performed on the interviews.

4B.1.2 Training and supervision

This is the first piece of qualitative research I have performed. In order to understand more of the process I attended 2 short interactive courses run by the University of Brighton entitled ‘Interview Skills’ and ‘Analysing Qualitative Data’. As my current supervisors are not specialised in qualitative research I also undertook to find an additional methodology supervisor. Dr Trevor Welland, a Lecturer in Medical Education (Research Methods), has extensive experience in qualitative research and runs the ‘Analysing Qualitative Data’ course at the university. Dr Welland helped me with the design of the topic guide and the coding framework for the interviews.

4B.1.3 Topic guide development

A topic guide was designed using relevant literature and after review of the paper questionnaire and study protocol (see Appendix 2). The topic guide covered questions around the logistics of the running the study including patient recruitment, interactions with other clinic staff and the impact of the timing of the clinic. It addressed the impact of the study on the CNS’s relationship with the participants and their interpretation of how the participants had experienced the study. Lastly it addressed the individual questionnaires performed in terms of whether the CNSs thought they were useful or added to their usual consultation.

4B.1.4 Conduct of the qualitative study

The semi-structured interviews with the CNSs were performed by myself and audio-recorded using a hand held recorder with the permission of the staff involved. As it was the researcher who had designed the study who was then looking for feedback, there was a risk of bias in the feedback given and potential conflict with the roles of PI and researcher in this position being performed by the same person and I thought long about how to reduce this conflict. In order to allow the CNSs to feel as comfortable as possible and to place them in a position of ‘power’, I travelled to their offices in the 3 sites and interviewed them individually in their usual surroundings. I was concerned that the CNSs would feel influenced by my position as a doctor and my relationship with the clinical teams they work with and addressed this by emphasising the confidentiality of the interview process before starting the interview. I wore

casual clothing without my hospital ID badge and made efforts to keep the atmosphere relaxed.

The interviews commenced with a reminder that the information was confidential and verbal consent given by the nurse that they were happy to proceed and to be recorded. They consented to anonymised quotes to be used by the researcher for the purpose of the study analysis and publication of results. The interview roughly followed the topic guide however was flexible and led by the CNS. I referred to the topic guide intermittently to ensure all pertinent areas were covered but mainly followed themes within the CNS's narrative. As the interviews progressed I used concepts that had been raised in previous interviews to see if these were themes that were experienced by all the participants across different sites. This was useful to see if particular topics were geographically specific or common across all areas.

4B.1.5 Transcription

I transcribed the interviews verbatim into Nvivo software. It was felt important that I transcribed the interviews rather than outsourcing to an external company in order to become intimately familiar with the data. Analysis in qualitative research is recommended to be performed as "an interpretive act rather than simply a technical procedure"[163]. Coughing and murmurs of assent were not transcribed in order to not interrupt the flow of the interview. However, where pertinent, laughter was recorded if it clarified the tone in which a point was made.

Nvivo is a software package which enables the researcher to store, organise and retrieve data efficiently. It does not provide any analysis function within the software but instead is useful to categorise source data into codes and themes without being methodologically specific[164]. Qualitative data analysis can be performed by printing out the transcripts and using colour coding by hand however I completed the online Nvivo training and found it a useful programme that was intuitive to use. It was crucial to have transcribed the interviews myself as I then had in depth knowledge of the text. Themes became apparent as I was transcribing which were then straightforward to analyse.

4B.1.6 Analysis

A number of different approaches were used for the qualitative analyses; thematic analyses for the interviews as the researcher wished to explore ideas and values raised by the CNSs rather than counting the responses they made (content analysis) or exploring hidden meanings and agendas (discourse analysis)[165]. The transcripts were analysed with a constant comparison method using a framework approach[166]. Framework analysis is commonly used in healthcare based qualitative research[167]. It is best used in scenarios where there is a specific research question, such as that outlined in the topic guide, which is used to form the starting point for data analysis, providing a structure from which new ideas and themes can arise from detailed analysis of the transcripts.

I formed an initial coding framework based upon the topic guide. The interviews were analysed line by line and initial areas assigned to the codes in the original framework. With detailed reading and interpretation of the interview, new codes emerged which were added to the coding framework. The constant comparison method was used so that each earlier interview was re-examined with the new codes that became apparent in later interviews. Thus an iterative approach was taken. This process was undertaken using Nvivo software.

This primary coding framework was then analysed and grouped into categories and themes, with care taken to note whether ideas were present across all sites or if there were areas where only certain individuals identified with certain codes. Contradictions within and between interviews were explored to aim for greater understanding of the themes involved.

The coding framework was submitted to Dr Welland along with a transcript of one interview. Dr Welland reviewed the coding structure and provided support in terms of developing hierarchy amongst the codes, leading to thematic analysis.

4B.2 Results

4B.2.1 Participant demographics

The participants involved in the qualitative analysis were the CNSs at each study site. There were 5 of these in total. In 2 sites there was a single nurse who conducted and managed the whole of the GOLDEN study in that site with some help from the clinical consultants. In 1 site there were 2 CNSs and 1 research nurse who were actively involved in the study and shared the work load between them, with the research nurse coordinating the study administration. These two methods of working affected the way the study was interpreted by the nurses in a number of ways which will be explored further in the thematic analysis below.

4B.2.2 Themes

There were a number of themes that emerged during the analysis of the transcripts and coding framework. A hierarchical structure was applied with overarching themes encompassing a number of different codes. Although there is always caution needed when applying results from a small number of centres to a wider population, these 3 sites differed widely in terms of geographical location, patient population and local resources and thus I believe the themes that emerge from the analysis of the transcripts are likely to be applicable to other NHS sites.

The primary outcome I was interested in was whether the geriatric assessment process was achievable within the confines of a busy NHS clinic. This was expressed in a number of different ways; general acceptability of the study, a focus on the practicalities of clinic time and organisation, the effect of repeated performances of the same assessments on the nurses' confidence and technique and the acceptability of the assessments to patients.

The general view from the CNSs was that they were happy to have been part of the study and found it a fulfilling exercise.

CNS02: I think overall it's been worthwhile and I'm really glad I've done it, really glad we've done it.

CNS04: I enjoyed doing the study, I was glad to be part of it actually

CNS05: it was a good, I would say it was an overall a good experience, I wouldn't say there was negative things about it that would make me apprehensive or not want to do something like that again

Effect on clinic time

One of the criticisms of performing a geriatric assessment is that it is time and resource consuming, however this is changing with the evolution of quicker screening tools and an increased use of patient reported outcome measure assessments[168]. A recently published qualitative study explored the cancer decision making pathways in the MDM and showed that consultants feel that nurses have the time to explore more complex needs of that patient that the patient is unwilling or unable to explain with themselves given the time constraints they work under[169]. We were investigating whether it was possible to perform a modified geriatric assessment by the CNSs without extra clinic staff and within the confines of a usual NHS outpatient clinic.

In terms of the effect on clinic time it was felt that, unsurprisingly, the assessments did add to the overall time the patient was spending in clinic.

CNS03: I used to tell the patients that it would take, it would mean they were there probably an extra 20 minutes but I think realistically it was probably a bit longer than that

CNS02: could you have managed the clinic better if you didn't have to do it? Yes, yes you could (laughs). But it didn't ever, it didn't ever stop us

CNS05: It did add a lot. I think it got easier the more you did

However the comment above of the process improving as time went on was also well expressed across all the sites

CNS02: I think the more you used it the quicker you got

I: So did things get easier as time went on?

CNS04: Yes they did, they did

CNS01: the first experience did worry me, however it turned out fine and so did the rest of it so it actually went ok but I was very dubious at the beginning

Acceptability to participants

A mixed methodology approach was used for the assessment of how acceptable the assessment process was to the participants. A questionnaire was completed by participants either directly after they had undergone the assessments or on a subsequent clinic visit. 37 (74%) of participants completed the questionnaires. The results are outlined in Table 4.14. 3 participants totally agreed that they found the questionnaires both tiring and distressing. For 2 of these participants they had ticked the last box for every section and afterwards in the comments box 1 had written *'happy to take part in anything that can help'* so it may be that there was an error in completing the form. The other participant however commented that *'after having a lot of difficult conversations before, I could not cope with it*'. The majority of participants reported that they had time to understand the study and answer the questions and were treated with respect throughout. 81% agreed that they would take part in a similar study again. Other comments made by the participants in the free text box included; *'I think it is a good thing to do'* and *'I am pleased to take part and hope this will help others in my position and cannot thank [the CNS] enough for her patience, understanding and positive support'.*

Table 4-14 Participant feedback

	Disagree N (%)	Partly agree N (%)	Neutral N (%)	Mainly agree N (%)	Totally agree N (%)
I was given enough time to read the patient information sheet and consent form and have my questions answered if necessary	0 (0)	1 (3)	1 (3)	2 (5)	33 (89)
I was treated with respect throughout the study period	0 (0)	1 (3)	0	3 (8)	33 (89)
I had enough time to complete the questionnaires comfortably	1 (3)	0 (0)	0 (0)	4 (11)	32 (86)
I found completing the questionnaires distressing	28 (75)	1 (3)	4 (11)	1 (3)	3 (8)
I found completing the questionnaires tiring	24 (65)	3 (8)	2 (5)	5 (14)	3 (8)
I would take part in another questionnaire based clinical trial such as this one	2 (5)	0 (0)	5 (14)	2 (5)	28 (76)

The CNSs were also asked how they thought the process had been for participants. This revealed some discord between sites as some CNSs felt more positively towards the experience than others. On closer questioning this was due to one negative experience which they then confessed coloured their view of subsequent participants. When they took an overarching viewpoint they felt that the majority of participants were happy to be part of the study.

> *CNS04: So overall the concept of doing research and helping is well received by patients, I think. You know particularly if they're well aware of what's that's being trying to achieve*

> *CNS05: I think they quite enjoyed having an actual task, they felt useful I think is probably the best word. They felt useful. I think. Because lots of people you meet have been told they can't work, they can't drive, you know they don't have a normal even daily activity in their lives so they actually almost felt quite proud of themselves*

‘They know they can’t do it’

An interesting aspect that emerged during the analysis of the acceptability to participants was the process of completing the questionnaires with participants of different level of function. The eligibility criteria for this study were relatively broad and therefore a wide scope of neurological impairment was witnessed. The subtler nuances of these impairments came across when performing the assessments in a way that was not picked up by the crude performance status criteria applied for eligibility and emphasises the importance of performing more detailed assessments. Nurses found that their interaction with the patients was very different depending on how highly functioning the patient was and the negative experiences some CNSs had undertaking the study with certain participants were related to the functioning level of that participant.

> *CNS03: I think it varied from patient to patient. I think the patients having radical found it fine, because they were high functioning patients so they didn’t find it difficult. I think the borderline patients are the ones you are looking to do, I think they’re the ones that struggled with it the most.*
>
> *I: Ok*
>
> *CNS03: Because they have, because the ones that are clear cut palliative care often didn’t have insight, so they might get really distressed at the time but afterwards basically forgot that they had got upset by it and didn’t find it, you know, I asked them afterwards how, you know ‘are you ok’ - they were fine, um, because they just couldn’t do it at all but they had no insight into that*
>
> *I: Yeah*
>
> *CNS03: I think the borderline ones were actually the ones that I found it hardest to do with*
>
> *I: Why was that?*
>
> *CNS03: Because they had enough insight to know they couldn’t do stuff*
>
> *CNS04: some of them get very upset about not being able to, being highlighted the fact that they can’t do things and that distresses them*

CNS05: patients got a bit frustrated with themselves or upset with themselves, which wasn't often, but the couple of occasions that happened it was quite bad, patients got quite distressed but that was because they were really cognitively very impaired

The effect on the participants of completing the questionnaires as witnessed by the nursing staff was not reflected in the participant feedback but it gives a valuable insight into the work CNSs do in supporting the psychological needs of patients. Often the neuro-oncology consultation is the first place where patients realise the true gravity of their diagnosis and the impairment it has caused. The sense of the oncology treatment process as a journey of which this consultation is the starting off point was prominent as participants come to terms with what their diagnosis means.

CNS01: they know, at that point in the conversation they've already been told that treatment is aimed at keeping them as well as they are now, but not improving them most likely. So it's also that realisation that this is all they've got, this is how he is

CNS02: they still felt that they weren't back to their normal selves, in inverted commas, but possibly, probably, weren't ever going to get back to that

Relationships

One of the most conflicting themes that emerged surrounded the effect of performing the assessments on the relationship between the nurse and the patient. A mixed methods qualitative study by the Royal College of Surgeons in Ireland in 2010 examined the role of the oncological CNS by performing focus groups with CNSs, healthcare professionals and patients. A key theme that emerged was that the CNSs felt a large part of their role was to contribute to the quality of life of their patients and provide support, both psychological support and educational - informing the patient about their condition[170].

This support system is embedded from the first consultation with the patient and some of the CNS participants in this study felt that that relationship was threatened by involving the patients in the study

CNS01: It sort of confused them, was that part of what I was doing? Was that part of their treatment? Was that part of what they were here for? I think it was a little bit confusing. So I had to really make it very clear that look, by the by, we're also doing this which I'm involved in, so they could separate me and the trial

I: OK

CNS01: And then they knew they would keep me, whatever, and I would support them but it was nothing to do with the trial and the trial was nothing to do with anything else

Once they began the assessments, two very different approaches were found and these seemed to depend on the set up of the site involved. At the site where there was a single nurse performing all the assessments she had often met the patient at a previous appointment, before they started doing the assessments. The process of the assessments then deepened that relationship.

CNS05: I actually think it probably improved, as, not a negative impact on the relationship but I think patients in general are very trusting, I think it's a nurse patient thing anyway, and they know by that point when you did the cognitive assessment that I was going to be following their care all the way through their initial treatment so we were already building up a good relationship so I think if anything it helped that.

CNS05: they'd already realised I was going to be the mainstay of support through their treatment

CNS02: I think you get the value out of doing the questionnaire with the patient because then you've got some connection with the study and with the patients as well.

In comparison, in the site where there were 3 nurses working, they tended to split up the assessments with each doing different parts of it. They also were performing them on the first meeting with the patients. This may be why a different interpretation was seen from that centre.

CNS03: that first consultation is all about making a relationship with the patient but actually what I was doing first was asking her a load of questions and getting her to do a load of things and then wasn't building that relationship so she already had a preformed idea of me before, and by the time I wanted to then try and build a relationship, she had kind of already disengaged with me

CNS04: I do feel that possibly if all this was done by the nurse then this could possibly impact on their relationship

A key part of this theme was the timing of the assessments, an aspect which was mentioned further in the 'future work' theme discussed later. In the centre where there were multiple members of staff one CNS commented

CNS01: With timing with the patients in hindsight I would want to discuss, if we did similar again, doing it on the second visit

However we realised that with these participants by the time of their second visit the treatment decisions have already been made and so to use the GA as a tool to assist with decision making it would not be appropriate at this time. In centres where the CNS is involved right from the start of the patient journey, in giving the results of surgery or in a pre-operative assessment there was more flexibility in the system

CNS02: it's been very individual with each patient how you capture them for the trial. I think partly because sometimes you were there when you were given the histology results so you could talk to them if that went well, and you could give them more information on top of what you'd already been discussing. Mostly we talked about it when they came to their first oncology appointment because it was so distressing for them to get those histology results so it was always quite hard

CNS05: I would either offer it at that point and I had a second opportunity that same week

CNS03: I could see how could make that work much better in that sort of environment where I saw them surgically and then saw them from the

oncology point of view because I already had a relationship with the patient, I could work out the right times to give them the information and, whereas here I did find that they came for the first time to [site involved] and then, not only are they getting all this masses of information, but we're then bombarding them with some study as well and I did find that that was quite a lot for them

If a GA is implemented it therefore needs to be done in a non-rigid way, where there is plasticity in the system to allow for how different centres work in terms of when the CNSs meet the patients and build their relationships with them.

Empowerment

An oncology clinical nurse specialist in the UK holds a highly specialised position however this role is often poorly defined. The National Cancer Action Team describes a CNS as a nurse who demonstrates highly developed skills in clinical skills and management as well as developing leadership and changing practice. On top of this they acknowledge that these roles are becoming increasingly complex, including providing psychological support to patients and specialist symptom control[171]. This is particularly true in the complex symptom burden experienced by neuro oncology patients. The role of the CNS can vary widely between tumour sites and between trusts and is often carefully worked out by the medical teams involved rather than a nationally unified job description. I was therefore interested in the theme that emerged around the relationship of the CNS to the consultants they work with and whether the geriatric assessment tool was needed or useful as a means of validating their opinion within the wider clinical team.

The overarching agreement between sites was that there was huge support from the consultants involved for each individual CNS in terms of running the study

CNS01: our consultants were completely and utterly on board

CNS03: They were perfectly supportive

CNS05: Very supportive. And happy, in some ways, overly happy for me to just carry on and not really require much input from them

However there were interesting points teased out when discussing the more abstract concept of a geriatric assessment in other settings. The CNSs voiced opinions that if it were a situation where the team were new, or the consultants were less disposed to trust the opinion of CNSs then the questionnaires could be vital. Also on deeper questioning they revealed that the questionnaires sometimes gave them more confidence in their own initial assessment

CNS03: If I come out and say to one of our registrars, who perhaps doesn't know me as well, I don't think, they won't listen to me necessarily unless I can show them something

CNS01: I wouldn't say to empower CNSs, I would say to empower whoever is doing the assessment on the patient, be it a doctor, a CNS, because if we're not around, um, and if it's new doctor and they go and speak to a consultant then it's going to empower them as well isn't it?

CNS05: Yeah it did give us confidence, it gave us all confidence to say look at that, there's something visual, something you can actually say, cos nurses are quite good at this gut feeling but it's quite difficult to convey that and explain that to clinicians. And often my assessment of someone's performance status is very different to a consultants' assessment

Future work

One of the key aspects of this study was to see whether the nurses felt that the process of a geriatric assessment was worthwhile and feasible within an NHS clinic. As discussed earlier, there was an impact on clinic time, and initially the nurses were reticent about whether they felt it was possible to perform this process regularly however this was often due to the misunderstanding that they would be performing this under a trial setting and collecting the toxicity data as well. The toxicity data collection was understood to be difficult to manage in terms of logistics, even in the centres where there were more staff. Once I

clarified it would just be the assessments then there was much more enthusiasm.

> *CNS01: I think an assessment is crucial……you know, that 10 minutes doing the MOCA, it tells you so much, we gain so much from that*
>
> *CNS03: think actually when, now that having discussed it, going back them, um, I think actually that is feasible*
>
> *CNS05: Yeah, I think it's that kind of information that we need to be assessing better, capturing, which is a difficult thing anyway*

Notably they saw that the assessment process had got easier as they went forward and that they felt it had helped towards their clinical judgement and processing. There was a widespread support for the idea of a geriatric assessment in principle

> *CNS05: Although your gut feeling is there, that's not really quite enough when you're making big decisions about people's treatment and potential outcomes, I think it's not enough, your gut feeling*

A key aspect in implementing a geriatric assessment, or indeed any new venture within medicine, is 'buy in'. The nurses emphasised that in order for people to perform it they needed to understand the relevance and importance of it. One nurse reported that in a different centre she had worked in the consultants were not interested in assessment tools:

> *CNS03: I did MOCAs and my consultants just laughed at it and went 'what the hell's that? I'm not interested in it'*

So in exploring the theme of future planning I asked them to give me their ideas of how they would structure a geriatric assessment given the experience on running the study and their support of it.

> *CNS01: Not too distressing for the patient, but is effective in highlighting their ability for treatment*
>
> *CNS03: It needs to be relevant, it needs to be understood why it's relevant by both whoever's doing it, and ideally it needs to be evident*

enough to relatives why it's necessary but if it's not, the person doing it needs to be able to explain to the relatives why it's relevant

I believe this last statement is a crucial point in expanding and embedding geriatric assessments within the neuro oncology cohort.

4B.2.3 Reflections

The process of qualitative analysis was fascinating and very different to previous quantitative research analysis I had performed. This part of the GOLDEN study involved a small number of participants however there was huge richness and depth to the interviews performed. It felt a privilege to be able to have time with the CNSs to explore in great detail the issues surrounding the running of the trial and an insight into the emotional effect of their jobs upon them. Inevitably with qualitative research there is the impact of the researcher's values and background on the discourse that occurs and I was very conscious that I was asking for feedback on a study that I had designed and led. This may have been mitigated slightly by the beginning of the interview where I emphasised that I was interested in their realistic feedback in order to improve the study for future work. The impression I had from the interviews was that there was a very honest approach in the CNSs' answers. These were, in the majority, not research nurses and so for some of them this was the first study they had had proper ownership over and were therefore keen to suggest ways that it worked or could be improved. I am interested in exploring qualitative research in future projects as I believe it gives invaluable insights into real world healthcare situations and may therefore enable change to be made more effectively.

The questionnaires for feedback from the clinicians involved were distributed at the end of the GOLDEN study however there was universal agreement across the 3 sites that the CNSs had performed the majority of the assessments and therefore the consultants did not feel it appropriate to complete the questionnaires.

4.3 Discussion

The GOLDEN study was a prospective feasibility study examining whether it is possible to embed a neurologically focused geriatric assessment within the confines of a busy NHS outpatient clinic across three sites. Although GAs have been used in larger oncology clinical trials, this is first time, to the author's knowledge, that it has been done with neuro-oncology patients.

The study met its primary outcome and proved, as assessed by recruitment rate, that this is a feasible process. Interestingly, there were a large number of patients who were thought to be eligible from MDM notes however on screening did not meet criteria. 2 patients did not have sufficient grasp of English, 9 patients lacked capacity and the rest fell into the exclusion criteria 'Patients unable to complete the questionnaires even with the help of a carer/member of trial team'. 3 patients had severe expressive and receptive dysphasia, 1 patient was felt to be too anxious and found the idea of the questionnaires too distressing, and the remaining 22 patients were too fatigued or had too poor a performance status to be able to consider completing the assessments. This is an interesting snapshot of the overall frailty of the patient cohort we are interested in.

In terms of the demographics of the study cohort; 80% of participants received surgery which is higher than the 60% quoted in national literature for the 70+ age group[7]. This is likely to be partly due to the inclusion of those aged 65-70 in this study (who made up 54% of participants) as well as the fact that the participants in GOLDEN had to be well enough to attend an oncology outpatient clinic and therefore those who were too unwell even to consider surgery were likely not to be eligible. 68% of the participants were ECOG PS 0-1, a similar group to the CCTG CE.6/EORTC 26062 trial however we also included 4 participants who were PS 3. This was unusual as most clinical trials use an ECOG PS of 2 as a cut off for eligibility and therefore we are reflecting a more realistic patient cohort than those usually enrolled in clinical trials.

There were no significant issues raised by the participants involved about the acceptability of the study and the overall feedback from the CNSs and clinicians showed support for the assessment process. Understandably there were certain

parts of the assessment which were more or less time consuming. The completion rates of the questionnaires differed slightly from site to site and informal feedback during the study period by the CNSs to the researcher suggested that the nurses' personal opinions on how useful they found the questionnaires or how taxing they felt they were to the participant then influenced the enthusiasm with which they attempted to complete them, the main area where this was most prominent was with the TMTB assessment. This emphasizes the need for the geriatric assessment process to be both relevant and understandable to participants and assessors in order for it to become accepted as standard practice.

The analysis of the study using univariable and multivariable cox regression techniques must be interpreted with caution as the study was not powered for these as primary end points. However, the effect of impaired mobility and an abnormal MoCA cannot be discounted and are worthy of further investigation on a larger scale. The results of the GA were not used to assess for treatment suitability within this study and it is unclear how much of the information was available to the clinicians at each site when treatment decisions were made. 7 of the 8 participants who used a stick were given active oncological treatment with 3 receiving palliative radiotherapy alone, 3 receiving dingle agent temozolomide and 1 receiving radical chemo-radiotherapy. However only 1 of the 4 participants using a frame or chair was given 40Gy in 15 fractions of radiotherapy alone, the remainder receiving best supportive care. It appears counterintuitive that using a frame had a significant impact on hazard ratio of death however using a chair did not. There are small numbers of participants within these two groups and so results must be interpreted with caution however there is a definite trend towards poorer outcomes with impaired mobility.

Of the 9 participants who received best supportive care, 5 had an impaired MoCA score and 4 a normal score. 23 out of the 28 participants who had an impaired MoCA score received active oncological treatment with 11 receiving palliative radiotherapy alone (6 30Gy in 6 fractions and 5 40Gy in 15 fractions), 4 receiving single agent temozolomide and 7 receiving radical treatment with

60Gy in 30# radiotherapy with concurrent and adjuvant temozolomide. Of those who received radical treatment, there were equal numbers of participants with normal and abnormal MoCA scores. This suggests that the MoCA score is a useful tool to be performed as it adds prognostic information that is not collected during a routine clinical assessment whereas it can be proposed that the effect of a walking aid has an impact on treatment decisions that is already in place.

Only 43% of those participants who were prescribed radical treatment with 60Gy in 30# of chemo-radiotherapy completed the treatment schedule including 6 months of adjuvant temozolomide. Of those who did there were equal numbers of normal and abnormal MoCA scores in each group. This is a similar proportion to those seen in the Stupp trial of 2005 which included all adults rather than just older patients and supports the idea that age alone should not be a prerequisite for not giving radical chemoradiotherapy regimes[38].

The overall prevalence of grade 3/4 toxicity levels in this cohort were 20% in those received radiotherapy or chemoradiotherapy. The majority of these patients experienced G3 fatigue (17%). This is slightly higher than the 6-10% reported in the radiotherapy arms of the NOA-08 and Nordic trials[39,55]. The publication of the CCTG CE.6/EORTC 26062 trial in the New England Journal of Medicine in 2018 did not include toxicity data for fatigue however their risk of thrombocytopenia was similar to ours in the temozolomide arm[56].

As was expected within this cohort, there were no cases of IDH1 mutated tumours found. As discussed in the literature review, IDH1 tumours are secondary GBMS, mainly evolving from lower grade astrocytomas and are less common in the older population. Of the patients whose MGMT testing was successfully performed, only 35% were found to show promoter methylation. This is slightly lower than some published data which suggests that MGMT methylation is not age dependent and occurs in roughly 45-50% of GBMs[22] however the NOA-08 study using single agent temozolomide showed similar promoter methylation prevalence[55]. The lower rate of methylation within our cohort may be why MGMT methylation status was not seen to be significant in univariable analysis for survival.

4.4 Conclusion

There are now a number of different treatment options available to older GBM patients, tested with randomized clinical trials, however the process of deciding on treatments for each individual participant is still unstandardized and subject to huge bias from the consultant or registrar seeing the patient. We have shown that a neurologically focused geriatric assessment is possible within an NHS clinic and that the results of a quick and simple cognitive screening tool can predict for survival, independent of treatment received. There is now an urgent need to refine the GA tool and embed it within larger randomized controlled trials in order to help provide a method for assisting clinicians in treatment decisions out with their gut feeling. There is also a discussion to be had surrounding the transformation of a geriatric assessment into a comprehensive geriatric assessment, involving multidisciplinary teams to input further support to this vulnerable patient cohort to see if outcomes can be improved with interventions.

Chapter 5 The use of MRI imaging to predict acute toxicity from cranial radiotherapy

5.1 Introduction

The majority of GBM patients over 65 who are actively treated by oncologists receive some form of radiotherapy to the brain. Short term side effects from radiotherapy include fatigue, headache, cognitive defects, nausea, weakness, hair loss and a need for increased steroid doses. Long term side effects include persistent cognitive defects, long term fatigue and hormonal imbalances[172]. Radiation causes an inflammatory response within the brain tissue as well as disrupting the blood brain barrier. It affects the vasculature of the brain with endothelial cell damage leading to microvascular dilatation, thickening of the vessel wall and increased risk of microbleeds and cerebrovascular accidents in the months to follow[173](171). There is a risk of inducing tissue necrosis from occlusion of small blood vessels within the brain parenchyma, leading to coagulation, focal necrosis and demyelination. Animal models have suggested radiation is cytotoxic to developing neuroglial progenitor cells with areas of stem cells such as the hippocampus and periventricular zones, particularly vulnerable to damage, leading to longer term neurocognitive decline[174,175]. There is evidence to suggest that radiotherapy can stabilise or improve functional ability for some older patients with GBM as well as providing a survival advantage however clinical experience suggests that the degree of side effects experienced and their impact on quality of life varies widely within this patient cohort.

The poor prognosis of older GBM patients leads to an emphasis on the need for focusing on quality of life when deciding on treatment regimes. We have pathological markers which can help us determine sensitivity of the tumour to chemotherapy, but we have no such guidance when it comes to making decisions about radiotherapy. If we were able to predict the degree of side effects likely to be experienced by a patient from radiotherapy treatment then it would enable us to make more individually tailored, patient centred treatment plans.

Risk factors for toxicities from radiotherapy include dose, fractionation and age however we have no more accurate ways of predicting which patients are likely to suffer significant side effects. MRIs can accurately detect microhaemmorhages and other ischemic changes which may correlate with a 'vulnerable' brain pre-treatment[63,176]. These MRI changes have been examined in Alzheimer and dementia research with correlations shown between MRI markers and disease severity[62]. As yet, they have not been used within the neuro oncology setting.

The aim of this chapter is to examine the relationship between MRI markers of a 'vulnerable' brain and the degree of acute side effects and change in quality of life amongst a population of older patients being treated with cranial radiotherapy for GBM. This was performed in two stages; initially a pilot study using a sub-group of the GOLDEN trial (those patients who underwent cranial radiotherapy). The promising results from this have been used to design a prospective cohort study with larger patient numbers and dedicated trial MRI sequences.

Results from the pilot study and the methodology for the currently recruiting larger study are presented here.

5A Part A - Pilot study

5A.1 Methods

5A.1.1 Study design

Participants in the GOLDEN study underwent standard diagnostic investigations for a GBM including an MRI scan, unless contraindicated. If participants were having surgery they then often also had a post-operative MRI scan to check for extent of resection and the presence of post-operative haemorrhage. During the GOLDEN study participants gave consent for their MRI scans to be accessed and analysed.

Ethical approval was awarded as part of the same application for the GOLDEN Study (West Midlands – Solihul Research Ethics Committee, reference number 16/WM/0408). Those participants who were eligible for the imaging section of the GOLDEN study were those who met eligibility criteria for GOLDEN as well as undergoing cranial radiotherapy as part of their oncological care pathway. Participants could also be treated with concurrent chemotherapy.

At the end of the study period, the pre-treatment MRI scans of those participants who met the eligibility criteria were anonymised and sent via the Image Exchange Portal (IEP) system to Dr Samantha Mills, consultant neuroradiologist, in Liverpool. As the participants in the study came from 3 different NHS sites, there were slightly different imaging protocols available for each participant. Therefore a complete analysis was not available for every participant. As this was a pilot study only, additional MRI sequences for research were not performed. Dr Mills was blinded to the results of the GOLDEN study and analysed each participant scan to assess the general health of the cortical brain matter. The study is interested in predicting the side effects of radiotherapy as related to the condition of the ‘normal’ cortex and so detailed analysis of the tumours was not performed. In order to assess cortical brain health, the following scoring parameters were used.[177]

5A.1.2 MRI scoring parameters

Tumour volume

If the pre-operative scan was available for transfer then the tumour volume was measured as a surrogate for radiotherapy field size. This was measured using a semi-automative process with the magic lasso feature on the CareStream PACS system overridden by manual corrections after review by the consultant neuroradiologist (SM). It was provided in mm^3.

Modified Scheltens white matter signal score

This score was developed from Fazeka's scale[178] and aimed to improve the inter and intra-observer variability of assessing white matter changes in that scale[179]. It includes the size and number of white matter changes, as well as regional information as to the location of the changes. It reflects the extent of small vessel disease within the brain which can lead to strokes, dementia, mood and gait disturbances[180].

The score involves a 3 point scoring system of 0-2 looking for periventricular white matter changes in each of the occipital, frontal and lateral periventricular areas; 0 being no changes, up to 2 for changes > 6mm. There is a maximum score in this section of 6. White matter signal hyperintensities are then examined in each of the frontal, parietal, occipital and temporal lobes, scoring between 0 and 6 depending on the size and number of them. This gives a maximum score for this section of 24. The total score is therefore out of 30 points and is assessed as a continuous scale. The Schelten's white matter signal score is designed to be applied to the entire cortex however in this study a modified version was performed on the contralateral hemisphere only to avoid tumour related changes. This technique of evaluating only the contralateral hemisphere has previously been applied in GBM [63].

Microbleed Anatomical Ratings Scale (MARS)

MARS is a continuous scale for assessing the presence of microhaemorrhage. Microhaemorrhage are small round hypointensities seen on T2* and susceptibility weighted imaging due to susceptibility artefact secondary to the presence of blood products. They are associated with advancing age and cerebrovascular disease and have been used as a biomarker for pathological

damage to small vessels within the brain[181]. The MARS score looks at the anatomical distribution to help differentiate amyloid and hypertensive aetiology. The presence of any microhaemorrhage is deemed to be pathological. They reflect disease burden of amyloid (if posterior fossa and grey-white matter junction) or microvascular disease/chronic hypertension (basal ganglia) [182]. For a series of set anatomical locations there is a binary classification of whether the bleeds were present or absent. Similar to the modified Scheltens scale, this was only applied to the contralateral cerebral hemisphere and posterior fossa to exclude microhaemorrhage and susceptibility artefact which may have occurred within the tumour.

Global Cortical Atrophy scale (GCA)

This scale was first developed in 1996 as a way of assessing cortical atrophy in post stroke dementia patients[183]. It has subsequently been further refined in general dementia research. Longitudinal studies have shown that gross brain volume decreases by around 0.2-0.5% and hippocampal volume (measured by the MTA score) by around 0.79-2.0% annually[184]. This process may be a normal part of ageing or accelerated by Alzheimer's disease.

The GCA scale is scored on a 4 point system from 0-3. Normal sulci have GCA grade 0, slight widening classifies as GCA 1, gyral volume loss is categorized as GCA 2 and pronounced widening of sulci with severe volume loss is GCA 3. Again, in the context of this study, assessment was made on the hemisphere contralateral to the tumour, to negate mass effect and sulcal effacement secondary to the tumour which may be masking underlying atrophy.

Medial Temporal lobe Atrophy scale (MTA)

The medial temporal lobe structures contain the hippocampus and parahippocampal region and are recognised to play a strong role in memory with atrophy of the lobe being associated with Alzheimer's disease. A method of scoring the decrease in volume of the medial temporal lobe was initially described by Scheltens et al in 1992. This has become a well validated scoring system, predominantly assessed in dementia research [185,186]. The assessment is conducted using a 5 point scoring system resulting in a total score of 0-4 with 0-1 being classified as normal. MTA 2 is pathological in patients under the age

of 70. MTA 3 is pathological in patients under the age of 80 and MTA 4 is pathological in all [187,188]. Contralateral temporal lobe assessment only was made and care was taken to determine the score was due to genuine atrophy rather than apparent volume loss secondary to hydrocephalus if the tumour was causing a degree of ventricular enlargement.

5A.1.3 Statistical analysis

Data was collated in Microsoft Excel and analysed using SPSS. The quantitative scores were provided to the researcher by Dr Mills and were examined using descriptive statistics. This was a small exploratory pilot section of the GOLDEN study and was not powered to look for significant correlations between scores and toxicity and survival. Analysis was done to see if any relationships were suggested which could help with the development of a larger study in this area. As the data was not normally distributed, there were some ordinal variables and there were small numbers of participants the correlation analysis was performed using the non-parametric Spearman's rank correlation coefficient.

5A.2 Results

5A.2.1 Data completeness

36 of the participants enrolled in the GOLDEN study received radiotherapy and therefore were suitable for inclusion into this exploratory pilot study. Their images were anonymised and transferred via IEP to Dr Mills in Liverpool who performed the pre-specified analyses.

As these patients were having routine diagnostic scans, there was a wide variety in the sequences used between NHS trusts. Not all the scoring systems were therefore able to be performed (see Table 5.1). MARS scoring was only possible for 61% of participants' scans. The MARS score is best performed on dedicated susceptibility weighted imaging but can also be assessed on gradient echo T2* weighted images. The latter sequence is performed routinely on patients undergoing diagnostic work up for a GBM in Brighton, but this was not standard in the other two trusts and therefore fewer participants had these sequences available.

Table 5-1 Completion rates of MRI scoring systems

Scoring system performed	N (%) [a]
Tumour volume	34 (94)
Modified Scheltens	33 (92)
MARS	22 (61)
GCA	34 (94)
MTA	34 (94)

[a]unless stated

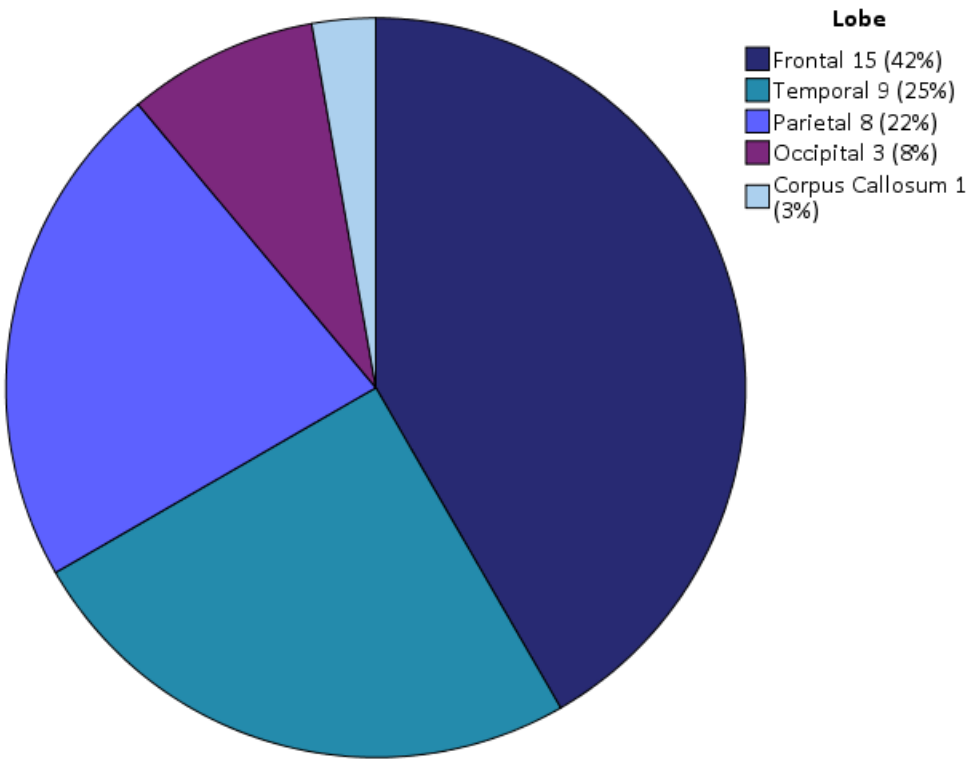
5A.2.2 Patient demographics

The median age of the group was 69 (IQR 66-72). 17 participants received palliative radiotherapy alone, with 6 (17%) having 30Gy in 6# and 11 (30%) having 40Gy in 15#. 19 participants received chemo-radiotherapy with 5 (14%) having 40Gy in 15# of radiotherapy and concurrent temozolomide and 14 (39%) having 60Gy in 30# of radiotherapy with concurrent temozolomide.

The study was open for a total of 17 months. At the time of censoring (12 weeks after the last participant completed treatment), 13 participants had died. Median overall survival was therefore not yet reached within the study. 3 and 6 month survival were 97% and 74% respectively.

21 (58%) participants had left sided tumours compared to 13 (36%) right sided and 2 (6%) with central or bilateral tumours. Of the 35 participants where the information was available, 27 (78%) had a tumour in a non-eloquent area whereas 4 (11%) were in the speech/motor strip and 4 (11%) were situated where vision would have been expected to be affected. The most common tumour location was the frontal lobe (see Figure 13). The median tumour volume was 24024 mm^3.

Figure 13 Distribution of tumours by lobe (original in colour)



This cohort overall had relatively good scores in terms of cortical brain health. The median modified Schelten's score was 4 (range 0-14) out of a maximum of 30, the GCA and MTA had median scores of 0 and when the MTA was modified

for age only 2 participants (6%) had an abnormal result. See Table 5.2 for the scoring characteristics.

Table 5-2 MRI scoring baseline characteristics

Scoring system		**N (%) [a]**
Tumour volume[b] mm^3		24024 (7517-41554)
Modified Scheltens[b]		4 (2-8)
MARS	No microbleeds	13 (59)
	Microbleeds present	9 (41)
GCA[b]		0 (0-1)
GCA	0	20 (59)
	1	13 (38)
	2	1 (3)
	3	0 (0)
MTA[b]		0 (0-1)
MTA	0	23 (67)
	1	5 (15)
	2	5 (15)
	3	3 (3)
MTA (age adjusted)	Normal	32 (94)
	Abnormal	2 (6)
[a]unless stated	[b] median (IQR)	

5A.2.3 Survival

This pilot study was not powered to detect significant associations between these 4 scoring systems and overall survival but instead exploratory analyses were performed to look for relationships and associations between cortical brain health and survival or toxicity from radiotherapy.

The researcher examined for relationships between tumour volume and the 4 quantitative MRI scores provided by Dr Mills with overall survival and toxicity, both grade 1-2 and 3-4 as measured by CTCAE. Survival was analysed using the Cox regression method for univariable analysis (see Table 5.3). An abnormal age adjusted MTA increased risk of death by 6.4 times (p=0.02),

where as having a GCA score of 1 (compared to normal) increased it 3.7 fold (p=0.04), and a score of 2 by 11.87 times (p=0.04).

Multivariate analysis was explored and various models created but due to the small number of participants in this pilot study and the low death rate at time of censoring, the models were over-fitted with variables and were not reliable enough to be reported.

Table 5-3 Cox regression univariable analysis for survival

Scoring system		Hazard ratio	p value	95% CI
Tumour volume		1.00	0.66	1.00-1.00
Modified Scheltens score		1.02	0.78	0.88-1.18
MARS	Microbleeds present	0.69	0.60	0.17-2.76
GCA (compared to 0)	**1**	**3.71**	**0.04**	**1.07-12.82**
	2	**11.87**	**0.04**	**1.18-119.72**
MTA (age adjusted)	**Abnormal**	**6.41**	**0.02**	**1.32-31.12**

5A.2.4 Toxicity

Toxicity data was collected at each follow up appointment for participants enrolled within this trial. As the trial did not involve a set follow up schedule, data was collected at different time points for each participant but only up to 12 weeks after the end of their primary treatment. Acute toxicity data was therefore complete for all participants involved in the study. 33 patients (92%) experienced grade 1-2 toxicity in at least 1 radiotherapy related domain of fatigue, headache, nausea, vomiting, seizures or confusion. As grade 1-2 toxicity is so common in this cohort, it may explain why there are no relationships to be found between degree of grade 1-2 toxicity and the MRI scoring parameters (see Table 5.4). G3-4 toxicity was only experienced by 7 patients (20%) and there was a significant correlation between both GCA score and age adjusted MTA score and degree of G3-4 acute toxicity (see Table 5.5). GCA has a correlation coefficient of 0.43 and MTA an even stronger one of 0.49. This suggests an important relationship with increasing toxicity associated with higher MTA and GCA scores. The MTA score was a binomial variable of

normal versus abnormal and therefore correlation testing may not be robust, This was therefore further investigated using Mann-Whitney *U* (two sample) non parametric test to examine for relationships between the MTA and GCA and G3/4 toxicity. This supported the conclusion that there is a significant relationship between GCA and the degree of toxicity experienced by participants (see Table 5.6)

Table 5-4 Spearman's rank correlation coefficient for grade 1-2 toxicity

Scoring system	r_s	p value
Tumour volume	-0.22	0.22
Modified Scheltens	0.08	0.64
MARS	-0.06	0.80
GCA	0.06	0.76
MTA (age adjusted)	0.08	0.66

Table 5-5 Spearman's rank correlation coefficient for grade 3-4 toxicity

Scoring system	r_s	p value
Tumour volume	0.30	0.09
Modified Scheltens	0.08	0.65
MARS	0.08	0.70
GCA	**0.43**	**0.01**
MTA (age adjusted)	**0.49**	**0.00**

Table 5-6 Mann Whitney U two tailed test

Null hypothesis (H_0)	p-value	Conclusion
The distribution of GCA is the same across categories of G3/4 toxicity	**0.03**	**Reject H_0**
The distribution of MTA is the same across categories of G3/4 toxicity	0.26	Retain H_0

The promising results from this pilot study were used to design the larger prospective cohort study. Due to the heterogeneity of different centres MRI

scanning protocols, funding was achieved to allow for a dedicated trial set of MRI sequences to be performed on those enrolling in the larger study. The design and methodology of this trial follows.

5B Part B – BRain Imaging to predict Toxicity in Elderly patients after Radiotherapy (BRITER study)

5B.1 Methods

5B.1.1 Study design

We designed a prospective, multicentre cohort study aimed at assessing whether there is a relationship between pre-treatment imaging markers of a vulnerable brain on MRI scans and a change in quality of life in the acute toxicity phase after cranial radiotherapy treatment. The study opened in July 2018 across 3 UK NHS sites and is aiming to complete recruitment by July 2020. Further UK sites are in the process of opening the study. The study was designed with the input of 3 separate consumer representative groups: the local Brighton and Sussex Consumer Representative Panel, The Brain Tumour Charity Research Involvement Network and the Brainstrust PPI panel.

The primary outcome measure is a change in quality of life from baseline to 8 weeks post radiotherapy treatment, as measured by the EORTC-QLQ C30, EORTC-BN20 and EORTC QLQ ELD14 questionnaires.

5B.1.2 Study setting

Participants are screened from patient lists during weekly multidisciplinary meetings (MDMs) involving neurosurgeons, neuro-oncologists, neuroradiologists, clinical nurse specialists, research nurses and allied health professionals across 3 NHS sites. These are currently: Brighton and Sussex University Hospitals NHS Trust in Brighton, The Beatson West of Scotland Cancer Centre in Glasgow and The Royal Marsden NHS Trust in Sutton. Sites that are due to open to recruitment include Addenbrookes Hospital (Cambridge), Norfolk and Norwich NHS Trust, Mount Vernon Cancer Centre (Northwood), Nottingham Universities Hospital, Castle Hill Hospital (Hull), Universities Hospital Birmingham and The Christie (Manchester).

Participants are approached and recruited when they attend for an outpatient neuro-oncology clinic appointment once a treatment decision has been made and eligibility criteria confirmed.

5B.1.3 Ethical regulations

Ethical approval has been granted from the London - Bloomsbury Research Ethics Committee, reference number 18/LO/0997. The Health Research Authority approval has been granted and local research and development agreement in place in all sites before the study opened. The study is sponsored by Brighton and Sussex University NHS Trust and adheres to Good Clinical Practice research guidelines. The participant information sheets (PIS) have been approved by the ethics board and provided to each participant if eligibility criteria are met. Each participant is given adequate time to read and understand what is involved in the study, including the chance to discuss it with a member of the study team before signing a consent form. The consent form is signed at the baseline visit prior to commencing the study. The participant's GP is made aware that the participant is enrolled on this study via a standardised GP letter that is sent by the trial team after the participant is recruited. The participant is aware and consents to this being done.

Non-substantial amendments have been made to the BRITER study after ethical approval had been granted to enable a change of PI at the non-sponsor site, the addition of extra sites to the study, a change in the eligibility criteria to exclude those participants who are being enrolled in CTIMP trials, and a change in the paperwork and logo of the study. Further details on the ethical approvals and the PIS can be found in Appendix 1.

5B.1.4 Eligibility criteria

Inclusion criteria

- Participants aged $\geq$ 65 years with a new diagnosis of GBM. Diagnosis made via histological confirmation following biopsy or debulking surgery or radiologically during an MDM meeting confirmed by a consultant neuro radiologist. This lower age limit is due to previous clinical trials which have established gold standard treatment regimes for patients under the age of 65. For patients aged 65 or over the evidence base to guide decisions making is sparser and treatment decisions are more nuanced with a greater emphasis on quality of life given the poorer prognosis in this cohort.

- Participants undergoing radiotherapy treatment to the brain for treatment of their GBM
- Participants able to undergo an MRI scan
- Participants undergoing treatment at one of the study centres
- Participants have capacity to participate in the study
- Participants with physical impairments that prevent them filling in their questionnaires involved in the study may still participate if they are able to communicate their answers though a third party

Exclusion criteria

- Participants not fit for radiotherapy treatment or having single agent chemotherapy with no radiotherapy
- Participants lacking capacity
- Participants who do not have sufficient grasp of the English language to be able to complete the questionnaires
- Participants unable to communicate their responses to the questionnaires
- Participants concurrently enrolled in a CTIMP study

5B.1.5 Study population and recruitment

Potentially eligible participants are identified from the weekly MDM meetings at each site involved in the study. Confirmation of a treatment decision involving cranial radiotherapy and that the participant meets the eligibility criteria is performed at the first neuro oncology outpatient appointment. The researcher is not involved in identifying participants apart from at the sponsor's site, thus decreasing the exposure to identifiable participant details. Participants are recruited in a consecutive manner.

The researchers were keen to involve multiple centres in the study to gain a good geographical spread in participant demographics and to improve recruitment. When the study was originally designed we did not account for participants potentially being enrolled in CTIMP studies, one of which is currently open in a number of centres across the UK. It was decided that participants who are enrolled in CTIMP studies would not be suitable for

enrolment within BRITER as there are too many unknown variables. Thus the predicted recruitment rates in each of the initial 3 centres in the study decreased slightly. The study was therefore opened up nationally and 7 further centres so far are in the process of opening.

5B.1.6 Study visits

Baseline visit

Baseline clinical assessment of the participants is conducted in the NHS neuro–oncology outpatient clinic setting. This involves completion of the EORTC-QLQ-C30 quality of life questionnaire with the BN-20 brain and ELD14 elderly patient subsets of questions added, the Montreal Cognitive Assessment and a record of the amount of corticosteroid the participant is currently taking. The EORTC-QLQ-C30 quality of life questionnaires are designed to be completed by the participant (they are allowed to ask for help from family/carer) and could therefore be taken home by the participant or completed in the waiting room rather than being completed within the clinic. There is a risk of the questionnaires not being filled in. We have therefore provided stamped addressed envelopes to be given to the participants in order to post the questionnaires back. The study team (who know the participant and would usually speak to them on the phone anyway during their treatment pathway) are able to call the participant to remind them to post back the questionnaires. The participants can be issued with new questionnaires to be completed at any point prior to starting their radiotherapy treatment. The MoCA is administered by a member of the study team either at the first outpatient appointment (baseline visit) or at another visit prior to the radiotherapy treatment commencing.

At the baseline visit details are also collected on age, gender, comorbidities, concurrent medications, performance status, social situation, surgery received and proposed treatment plan. The participant's treatment plan is not affected by participation within the study.

Follow up visits

Once the participant has completed their radiotherapy (with or without concurrent chemotherapy) treatment, they attend for a 4 week and 8 week follow up visit (plus or minus 1 week for each to allow for flexibility). These visits

are part of their usual care plan within the NHS follow up schedule. When they attend they repeat the EORTC quality of life questionnaires and MoCA questionnaire as well as having assessment of their CTCAE radiotherapy toxicity score and steroid use. If the patient is unable to attend, the reasons why will be documented by the trial team. If possible, the EORTC questionnaires can be posted to the patient to complete and return by post. As we are keen to try and capture the population as a whole, there was concern that those patients who suffer worse side effects from radiotherapy may be lost to follow up and their data not analysed. Although this is still possible, we hope to capture as much information as possible by the postal system of competing the questionnaires or the details from the study team, as recorded in the CRF, if they do not attend. Members of the study team are permitted to phone the patient to remind them to complete the questionnaires if they are not returned or can complete them over the phone with the patient. After the 8 week follow up appointment, participation in the study is complete.

5B.1.7 MRI scans

In most cases, the participant will have undergone an MRI scan with contrast as part of their usual care plan prior to attending the neuro-oncology clinic. If the routine scan has the required imaging sequences needed for the BRITER study then no further scanning is required. This is assessed by the neuro oncology clinician during the outpatient clinic appointment or the neuro radiologist at the MDM or a member of the study team prior to the appointment. A list of the required sequences is readily available for the study team during this process. If not all of the required sequences have been done then the patient will undergo a further MRI scan. This is performed prior to the participant starting radiotherapy treatment but should not delay the start of the treatment.

MRI scans are the imaging modality of choice in neuro-oncological management. This modality utilises strong magnetic fields and radiowaves to produces high resolution images of the brain due to the relaxation of protons within tissue. This is a non-ionising imaging technique and therefore does not increase the radiation exposure to patients.

The MRI sequences required for the trial are as follows:

- Axial T2
- Volumetric T1 pre contrast
- Post contrast volumetric T1
- DWI/ADC
- Susceptibility weighted imaging
- Axial T2* gradient echo

  3D volumetric inversion recovery or MP-RAGE (additional sequence - to allow accurate quantification of cortical thickness/volumes using Freesurfer software in addition to scoring methods of atrophy – if this had not been acquired as part of a centre's standard volumetric sequences)

The anonymised MRI scans are sent to Dr Mills, consultant neuro-radiologist at The Walton Centre, Liverpool for analysis. She will assess the scans and provide the same imaging scores as outlined earlier in the pilot study methods section, in addition to formal quantification of cortical thickness of the contralateral hemisphere (using Freesurfer software).

5B.1.8 Questionnaires

EORTC QLQ-C30

The EORTC QLQ-C30 was first developed with palliative lung cancer patients in 1986 for use as an integrated, modular approach to measuring quality of life in patients enrolled in clinical trials. It involves a self-reporting questionnaire which incorporates five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, nausea and vomiting); and a global health and quality of life scale[189]. Since its publication in 1993, the questionnaire has been translated into over 100 languages and validated in around 3,000 studies worldwide. The current version is 3.0 which was used in this study (see Appendix 2 for more details). The EORTC QLQ C30 questionnaire is excellent at capturing a general quality of life picture however a modular approach was then adopted by the EORTC as they recognised that different cohorts of cancer patients have different needs and experience unique symptom burdens.

EORTC QLQ-BN20

The EORTC QLQ-BN20 is a module specific to brain neoplasms which was developed in English in 1996[190] and subsequently validated in international trials[191]. It consists of a self-reporting questionnaire of 24 items, comprising of 5 scales and 7 single items. There is some cross over between the emotional scale in the BN20 and C30 questionnaires and it has been suggested this could be omitted in one questionnaire however in general they are designed to be used in conjunction with each other (see Appendix 2).

EORTC QLQ-ELD14

Many of the EORTC modules were developed in younger patients and therefore the ELD14 module was validated and published in 2012 in order to reflect the particular age specific concerns in this cohort [192]. It consists of a self-reporting questionnaire made up of 5 scales (illness burden, mobility, maintaining purpose, worries about others and future worries) and 2 single items (family support and joint stiffness). It is designed to be used in conjunction with the EORTC QLQ-C30 questionnaire (see Appendix 2).

Montreal Cognitive Assessment (MoCA)

As described earlier in this thesis, the MoCA is a widely used and well validated cognitive screening tool which tests several cognitive domains and results in a total overall score of 30. A score of below 26 is considered abnormal. Results from the GOLDEN study (see Chapter 4) have shown that an abnormal MoCA score can independently predict for poorer overall survival within this age range of patients.

5B.1.8 Clinical details

The clinical details collected from the patients at their baseline visit will be recorded by the trial team. For background demographics age and performance status will be documented. In order to ascertain pre-treatment factors that may affect prognosis, the surgery performed will be noted. Results from the GOLDEN study have shown that mobility was an important factor in determining outcomes in this cohort and so details of walking aids will be gathered. Comorbidities will be assessed using the Charlson Comorbidity Index and comedications (including steroid dose) recorded.

5B.1.9 Toxicities

Toxicity data will be collected at the 4 week and 8 week follow up visits using the Common Terminology Criteria for Adverse Events (CTCAE) scoring system V5.0[193]. These criteria are used for the management of chemotherapy administration and dosing, and in clinical trials to provide standardisation and consistency in the definition of treatment-related toxicity. Documentation of fatigue, headache, nausea, vomiting and seizures are collected as well as a free text box on the CRF for any other symptomatology.

5B.1.10 Statistical considerations

The primary outcome of this study is change in quality of life from baseline to 8 weeks post radiotherapy treatment. The data from the pilot work in the GOLDEN study was not available at the time of designing the BRITER study and therefore sample size calculations have been performed assuming a clinically significant end point of a 10 point change (SD=22.1 taken from the EORTC website reference guide) in EORTC QLQ questionnaire score between baseline and 8 weeks[194]. Estimated sample size for one-sample comparison of proportion to hypothesized value assuming a 2 sided alpha of 0.05 and power of 0.9 gives a sample of 73. However, allowing for 20% attrition in questionnaire completion, this results in a sample size of 91. With 73 participants at 8 weeks, we will have 90% power for 5% significance to detect 5% of participants achieving a 10 point change in QoL. However, this small a proportion will only allow us to fit one variable in the model. It has therefore been recommended by the statistical team to aim for a recruitment target of 100 participants in order to fit the 4 MRI variables to the model.

5.2 Discussion

Radiotherapy can worsen small vessel disease by causing microvascular occlusion and therefore it is theorised that the background level of small vessel disease may correlate with the severity of radiotherapy induced toxicity. A previous small study using the modified Schelten's score to assess for white matter changes in the contralateral hemisphere in GBM patients aged 50-73 found a median score of 14 (range 6-25)[63]. Our median of 4 (range 0-14) showed the cortical brain health of the contralateral hemisphere in this cohort to be relatively good compared to a normal population with overall low scores for white matter lesions, microhaemmorhages and atrophy.

Within this pilot study, 15 (42%) had a diagnosis of a cardiovascular comorbidity including ischemic heart disease (3, 8%), hypercholesterolaemia (4, 11%) and hypertension (11, 31%) for which they were on appropriate medications. These are in line with national figures for this age range and suggest we have a representative patient cohort[195] however the cortical brain health was better than expected. Lower socioeconomic status has been linked to a higher risk of stroke and to the development of dementia[196,197], processes mirroring the changes seen on MRI that we are measuring in this study. An assessment of the socioeconomic status of the participants was achieved using the first part of their postcode and the UK national deprivation index map. The median deprivation decile are measured from 1-10 with 1 representing areas with highest level of socio-economic deprivation and 10 representing the least deprived areas. The median decile score for this cohort was 8 (IQR 5.0-9.0) suggesting that overall this group of patients was in a higher socioeconomic group compared to the national average. This may be a factor in explaining the improved cortical brain health in this cohort.

The relevance of the presence of microbleeds as quantified using the MARS scoring system was not able to be analysed due to the low number of T2* and susceptibility weighted image sequences performed routinely within NHS imaging protocols. There is a known relationship between the development of microbleeds and exposure to cranial radiotherapy and microbleeds have been used as a marker for radiation induced microvascular injury leading to cognitive

decline[198,199]. It is therefore theorised that the presence of a high burden of microbleeds prior to radiotherapy treatment may lead to accelerated cognitive decline and impact of quality of life. The development of the BRITER study, with a dedicated trial scan with pre-specified MRI sequences, will enable us to provide more formal quantification of cortical thickness and atrophy and assess the role of microhaemorrhage scoring in a larger cohort of patients.

Medial temporal lobe atrophy and global cortical atrophy have both been used extensively in dementia research. MTA is known to both diagnose Alzheimer's disease and to predict progression to dementia in those with mild cognitive impairment[200]. There is little work as yet using MTA and GCA scores to help predict radiotherapy toxicity however cortical thinning and atrophy has been shown to be an effect of high dose cranial radiotherapy and appears to be radiation dose dependent[201]. This supports the theory that if there is pre-existing cortical thinning then the degree of toxicity would be expected to increase. Our study, although limited by the type of scans performed routinely within the NHS and the low numbers of participants, has suggested the presence of a relationship between GCA and MTA scores and both overall survival and acute toxicity experienced by participants. This is a small study and there is a risk of over interpreting the survival data however, as a pilot, it has been successful in exploring the relationships between these markers and has shown the feasibility of using pre-treatment MRI scans for analysis. The BRITER study will now enable us to explore these relationships further, with more detailed MRI sequences and greater patient numbers, and hopefully allow us to predict which patients are likely to suffer significant acute toxicities from radiotherapy to the brain.

5.3 Conclusion

Radiotherapy to the brain is known to have significant short and long term consequences. In the older GBM patient group, the survival benefits of treatment must be measured against the effect on quality of life from the side effects of treatment. We can now use MGMT promoter methylation status as a way to guide chemotherapy treatment decisions but as yet no such biomarker is available to influence decisions about radiotherapy. The pilot study presented

here suggests that there is a relationship between Global Cortical Atrophy and Medial Temporal Lobe Atrophy scores and survival as well as the likelihood of G3 to 4 acute toxicity from cranial radiotherapy. The BRITER study aims to explore whether that relationship is confirmed within a larger patient cohort and, more importantly, whether that has a significant effect on patient quality of life. We aim to enable clinicians to make patient centred, individualised treatment plans in the future based on the particular risk benefit profile of each treatment option available within this vulnerable patient cohort.

Chapter 6 Study conclusions and future directions

6.1 Summary of findings

We here present a comprehensive literature review covering the evidence base behind current assessment and treatment strategies for older glioblastoma patients. There has been a moderate increase over the last decade in the prevalence of clinical studies aimed specifically at older GBM patients, which have validated the use of single agent chemotherapy, radiotherapy or combined chemo-radiation as appropriate treatment strategies within this cohort. From these studies, molecular markers have been used to stratify treatment regimens. The literature review has shown that certain clinical characteristics, such as presenting with seizures, cognitive defects or particular comorbidities are associated with survival outcomes in older GBM patients, alongside social situation and marital status. However, the methods to clinically assess this patient cohort have not been examined in depth in the international literature. In particular, for this older group of patients, the review showed that the use of geriatric assessment tools, which have proved instrumental in stratifying patients other tumour types, have not yet been utilised within the neuro oncology community.

The retrospective cohort study presented in this thesis represents a large tranche of patients with ‘real world’ data. The data is relevant to current national practices and involved three different cancer centres with a wide geographical spread. The survival outcomes in this group were similar to those reported from national database interrogation, showing a representative cohort. The depth of the data we achieved in this study through detailed analysis of all hospital records and patient notes available enabled us to show that increasing age was not an independent prognostic factor once performance status and treatment regimens were accounted for. We aimed to explore whether pre-treatment characteristics could predict for overall survival. Clinically we showed that ECOG performance status and presenting with seizures had a significant effect on overall survival, and radiologically, unifocal disease or disease confined to the cerebral hemisphere both significantly improved overall survival irrespective of treatment received. Although the study is subject to the limitations common to

all retrospective work, this study is, to the authors' knowledge, the largest UK-based retrospective review incorporating details of clinical presentation, comorbidities and imaging characteristics within the older cohort of GBM patients and can be used to inform clinical practice.

The survey generated the first published data on neuro-oncology consultants' working practices with older GBM patients within the UK. A response rate of 60% validated the results given. Although work has suggested that ECOG performance status is a crude measure of patient fitness, the majority of neuro oncology consultants surveyed reported it as a 'very important' factor in determining treatment options, concurring with the retrospective work performed in the previous chapter. Our results revealed heterogeneity in oncological services in terms of referrals from MDTs and availability of physiotherapy, occupational therapy and speech and language services. Overall the study showed that there is little current uptake in the use of cognitive assessment or geriatric assessment tools within the UK and little multidisciplinary assessment of this difficult to treat cohort.

The prospective multicentre feasibility study (GOLDEN study) was, to the author's knowledge, the first aiming to embed a neuro-oncologically focused geriatric assessment screening process within the UK outpatient setting. The study aim was to determine whether, without extra funding or resources, it was acceptable to participants and staff for these assessments to be performed. It recruited within the pre specified time frame and met its primary outcome of recruitment rate over 80%. Qualitative interviews with the nursing staff gave an in depth analysis of the process of the assessments and feedback on the individual questionnaires themselves; these comments explained the differing completion rates for the different elements of the geriatric assessment tool. We have highlighted the need for the relevance of any geriatric assessment tool to be understood by those performing it in order to achieve engagement with the process. The study achieved its stated aim and showed that a neuro oncologically focussed geriatric assessment screening process is feasible within a UK neuro oncology outpatient clinic. Although the study was not powered to detect the prognostic implications of different tests, there was a strong

relationship shown between both baseline level of mobility and their cognitive state (as measured by the MoCA) and overall survival. This now needs to be explored in a larger cohort.

The final piece of work was an exploratory pilot study examining the relationship between 5 MRI based scores measuring the level of normal brain ischemia and damage, and the overall toxicity and outcomes of the participants after radiotherapy. The pilot study was limited by a small sample size and the type of MRI sequences performed as they were subject to the individual scanning protocols performed routinely in each NHS trust. Despite this, a strong relationship between Global Cortical Atrophy and Medial Temporal Lobe Atrophy scores and grade 3-4 toxicity was shown. This work is continuing and a prospective study is currently recruiting.

6.2 Unanswered questions and future directions

The initial results from the centralised review of archived pathological samples which was performed as part of the retrospective cohort study were disappointing in that there were no significant prognostic implications (differing from results seen in other studies). However, further analysis of these samples using Illumina Beadchip CpG methylation techniques is being undertaken in collaboration with researchers at Queen's University Belfast. Previous published studies have suggested an age dependent effect of certain genetic mutations however this tends to be in unselected adult populations. This will provide one of the largest group of older GBM patient samples. The pathological analysis being undertaken involves detailed examination of CpG methylation patterns. The group will explore whether there are particular subsets of GBMs within the older population, and whether they differ significantly from the younger adult GBM population as studied in The Cancer Genome Atlas repository. It is hoped this analysis will be more fruitful than the work done so far within this thesis and the researcher will be liaising closely with the team in Belfast. Results are expected in the next 2 years.

The data from the pilot imaging study has shown a strong relationship between certain MRI scores and overall survival and toxicity. This is now being explored in the BRITER study, a large prospective multicentre study with dedicated trial

MRI scan sequences to ensure greater sensitivity in the scores. This aims to complete recruitment in August 2020 and results will be published shortly after. If this study confirms the work seen in the pilot study then it will provide an imaging biomarker to aid clinicians to assess the likely chances of severe side effects from radiotherapy, and help guide treatment decisions. The researcher is Chief Investigator for this study and is in the process of opening more sites. The analysis and publication of this data in 2020 will enable future directions of imaging studies within this age group to be developed. Discussions are also in place between the researcher and neuro radiologists in Edinburgh about collaborating in a study to assess the potential effect of baseline sarcopenia in older GBM patients. Sarcopenia has become an interesting biomarker of biological age amongst geriatric oncology studies in other tumour sites but as yet has not been explored within neuro-oncology. The researcher hypothesises that it would not prove to be significant in the same way in neuro-oncology patients, due to the underlying aetiology of their frailty being secondary to cognitive dysfunction rather than physical dysfunction. This work carries on in development.

The survey performed has shown a lack of MDM support within the outpatient setting. The progression from a geriatric assessment is a comprehensive geriatric assessment, with interventions performed guided by the individual patient deficits found. It was beyond the scope of this thesis to explore whether a comprehensive geriatric assessment could alter the prognostic implications of geriatric screening tools but that would be a fascinating future study. Evidence in other tumour sites has suggested that early intervention is the best way to improve outcomes and there is work to be done in exploring whether pre-operative MDM assessment and intervention would be more effective than post-operative.

There is heterogeneity in the types of assessment performed under the umbrella of ‘geriatric assessment’. We created the neurologically focussed screening tool used in the GOLDEN study on the basis of a thorough literature review examining the evidence base behind all of the tools used previously in this cohort. However there are few studies looking at geriatric assessment tools

within the neuro oncology patient group and it may be that those used within the GOLDEN study were not the most appropriate. The MoCA has shown a significant relationship with survival and should be now used routinely in all neuro oncology clinics but the TMTB was poorly completed and did not add any significant prognostic information and could be omitted. The GOLDEN study has shown that performing a geriatric screening assessment is feasible within the outpatient neuro oncology setting however further work is needed to validate this process within a larger patient cohort and explore in greater detail the prognostic effect of the scores in order to help clinicians and patients in their treatment decision making. The researcher is a student member of the National Cancer Research Institute Brain Clinical Studies Group. This groups aims to shape the way that research is performed in neuro-oncology across the UK and has close links to The Brain Matrix. Access to this group provides an excellent opportunity to discuss incorporating a geriatric assessment into every adult neuro oncology trial being set up within the UK and on all those patients enrolled in the Brain Matrix. This would enable data to be collected on a much larger scale and provide a platform to start conversations about interventions to improve the holistic management of older GBM patients, as performed by neuro-oncologists, empowering them to make simple changes to their patients management without needing the complex involvement of specialised geriatricians. The researcher is also part of the Tessa Jowell Brain Cancer Mission, having been invited to take in a role in Strand 3 “New Roads in Training”. This group aims to create a series of 12 month fellowships within the UK, primarily aimed at clinical oncology trainees who have an interest in becoming consultant neuro-oncologists. The researcher is involved in developing the curriculum for these fellowships and looking to expand training opportunities to the wider field outside of clinical oncology. This provides an excellent opportunity to embed the principles of geriatric neuro-oncology within this specialised training programme, effecting the way that a new generation of neuro-oncology consultants will approach their older patients.

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Chapter 8 Appendix 1: Ethical Approval Documents, Patient Information Sheets, Consent Forms and GP letters

Figure 14: REC approval for The influence of clinical and tumour characteristics on survival outcomes for older patients with glioblastoma

NHS
Health Research Authority
South Central - Berkshire B Research Ethics Committee
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1385

23 November 2015

Dr Juliet Brock
Sussex Cancer Centre
Eastern Road
Brighton
BN2 5BE

Dear Dr Brock

Study title:	**What is the clinical and biological significance of MGMT methylation, IDH1mutation and further pathological screening tests in glioblastoma multiforme in over 70 year olds?**
REC reference:	**15/SC/0742**
Protocol number:	**n/a**
IRAS project ID:	**188170**

The Proportionate Review Sub-committee of the South Central - Berkshire B Research Ethics Committee reviewed the above application on 23 November 2015.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Tina Cavaliere, nrescommittee.southcentral-berkshireb@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

On behalf of the Committee, the sub-committee gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion").

Approved documents

The documents reviewed and approved were:

Document	*Version*	*Date*
IRAS Checklist XML [Checklist_19112015]		19 November 2015
Other [Previous REC submission response]		27 October 2015
REC Application Form [REC_Form_17112015]		17 November 2015
Research protocol or project proposal [Trial protocol]	1	14 October 2015
Summary CV for Chief Investigator (CI) [CI summary CV]	1	14 October 2015
Summary CV for student [student CV]		19 November 2015
Summary CV for supervisor (student research) [Supervisor's CV]		19 November 2015

Membership of the Proportionate Review Sub-Committee

The members of the Sub-Committee who took part in the review are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

15/SC/0742	Please quote this number on all correspondence

Yours sincerely

Pp

Dr John Sheridan
Chair

Email: nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

"After ethical review – guidance for researchers"

Copy to: *Mr Scott Harfield, R&D*

South Central - Berkshire B Research Ethics Committee

Attendance at PRS Sub-Committee of the REC meeting on 24 November 2015

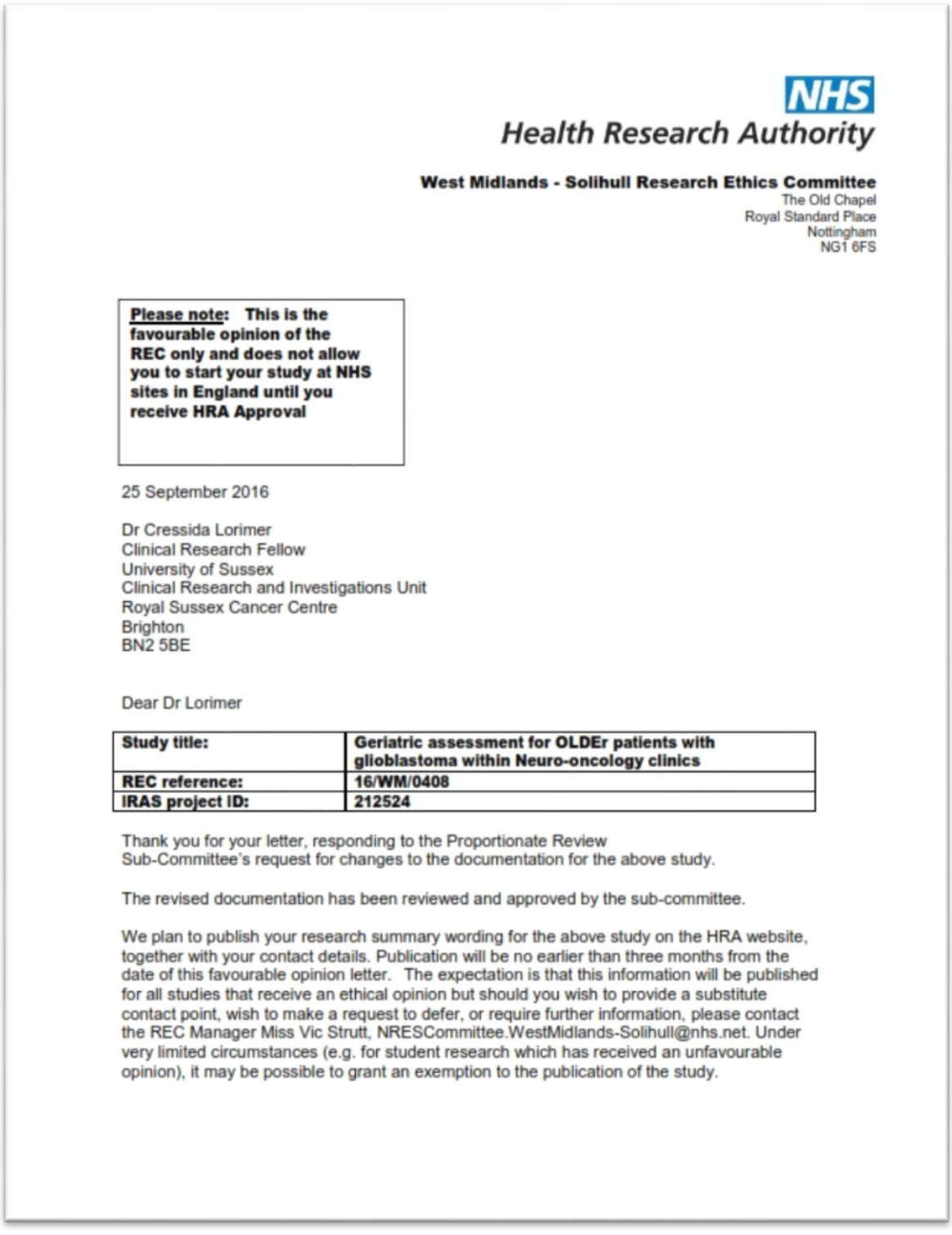
Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr Mike Arnott	Research Consultant	Yes	
Dr John Sheridan (Chair)	Consultant Toxicologist and Chemist	Yes	
Mrs Mary Sneade	Clinical Trial manager	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Tina Cavaliere	REC Manager

Figure 15: Ethical approval for GOLDEN study



NHS
Health Research Authority

West Midlands - Solihull Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

25 September 2016

Dr Cressida Lorimer
Clinical Research Fellow
University of Sussex
Clinical Research and Investigations Unit
Royal Sussex Cancer Centre
Brighton
BN2 5BE

Dear Dr Lorimer

Study title:	**Geriatric assessment for OLDEr patients with glioblastoma within Neuro-oncology clinics**
REC reference:	**16/WM/0408**
IRAS project ID:	**212524**

Thank you for your letter, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Vic Strutt, NRESCommittee.WestMidlands-Solihull@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Conditions of the favourable opinion

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" above).

Approved documents

The documents reviewed and approved by the Committee are:

Document	*Version*	*Date*
Covering letter on headed paper [Covering letter]	1.0	16 September 2016
GP/consultant information sheets or letters [GP letter]	0.1	16 September 2016
IRAS Application Form [IRAS_Form_05092016]		05 September 2016
IRAS Checklist XML [Checklist_16092016]		16 September 2016
Letter from funder [Letter from funder]	1.0	31 July 2016
Letter from sponsor [Letter from sponsor]	0.1	24 August 2016
Non-validated questionnaire [Participant feedback form]	1.2	27 July 2016
Non-validated questionnaire [Trial team feedback form]	1.2	27 July 2016
Other [Schedule of Events]	1.0	01 August 2016
Other [Statement of Activities]	1.0	01 August 2016
Other [Patient and public feedback]		16 September 2016
Participant consent form [Consent form]	0.4	16 September 2016
Participant information sheet (PIS) [Patient information sheet]	0.6	16 September 2016
Referee's report or other scientific critique report [Initial sponsorship committee feedback]	1.0	11 August 2016
Research protocol or project proposal [Protocol]	0.7	16 September 2016
Summary CV for Chief Investigator (CI) [CI CV]	1.0	28 July 2016
Summary CV for student	1.0	28 July 2016
Summary CV for supervisor (student research)	1.0	28 July 2016
Validated questionnaire [Questionnaire pack]	0.1	26 July 2016

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports

- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/WM/0408	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

pp. V. Swain

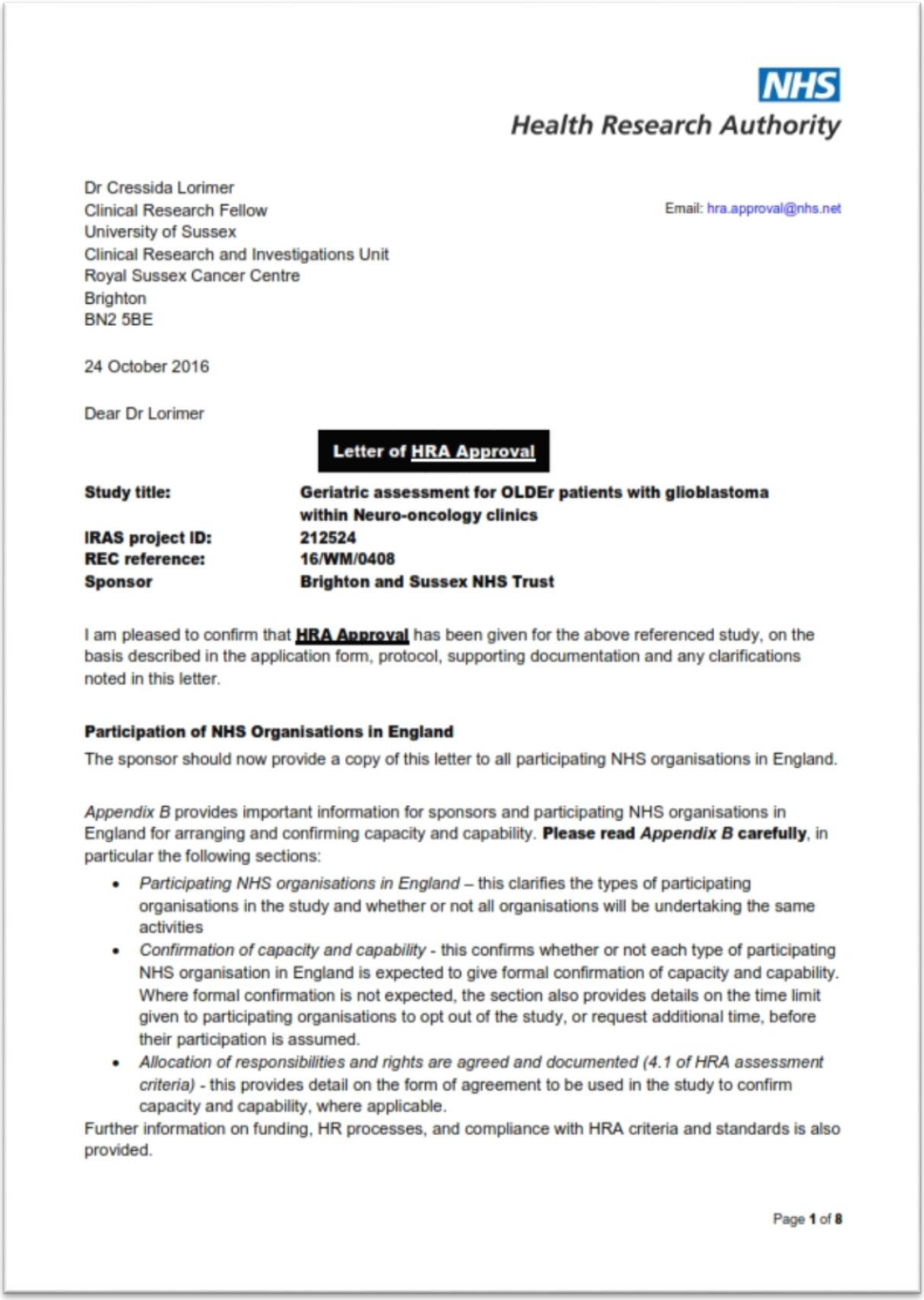
Dr Rex J Polson
Chair

Email: NRESCommittee.WestMidlands-Solihull@nhs.net

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *Mr Scott Harfield*

Figure 16: HRA approval for the GOLDEN study



NHS
Health Research Authority

Dr Cressida Lorimer
Clinical Research Fellow
University of Sussex
Clinical Research and Investigations Unit
Royal Sussex Cancer Centre
Brighton
BN2 5BE

Email: hra.approval@nhs.net

24 October 2016

Dear Dr Lorimer

Letter of HRA Approval

Study title:	**Geriatric assessment for OLDEr patients with glioblastoma within Neuro-oncology clinics**
IRAS project ID:	**212524**
REC reference:	**16/WM/0408**
Sponsor	**Brighton and Sussex NHS Trust**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

Page **1** of **8**

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please email the HRA at hra.approval@nhs.net. Additionally, one of our staff would be happy to call and discuss your experience of HRA Approval.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **212524**. Please quote this on all correspondence.

Yours sincerely

Dr Claire Cole
Senior Assessor

Email: hra.approval@nhs.net

Copy to: *Mr Scott Harfield, Brighton and Sussex University Hospitals NHS Trust (Sponsor Contact and Lead NHS R&D Contact)*

NIHR CRN Portfolio Applications Team

IRAS project ID	212524

Appendix A - List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [Covering letter]	1.0	16 September 2016
GP/consultant information sheets or letters [GP letter]	0.1	16 September 2016
IRAS Application Form [IRAS_Form_05092016]		05 September 2016
Letter from funder [Letter from funder]	1.0	31 July 2016
Letter from sponsor [Letter from sponsor]	0.1	24 August 2016
Non-validated questionnaire [Participant feedback form]	1.2	27 July 2016
Non-validated questionnaire [Trial team feedback form]	1.2	27 July 2016
Other [Schedule of Events]	1.0	24 October 2016
Other [Statement of Activities]	1.0	24 October 2016
Other [Patient and public feedback]		16 September 2016
Participant consent form [Consent Form]	0.5	18 October 2016
Participant information sheet (PIS) [PIS]	0.7	18 October 2016
Referee's report or other scientific critique report [Initial sponsorship committee feedback]	1.0	11 August 2016
Research protocol or project proposal [Protocol]	0.7	16 September 2016
Summary CV for Chief Investigator (CI) [CI CV]	1.0	28 July 2016
Summary CV for student	1.0	28 July 2016
Summary CV for supervisor (student research)	1.0	28 July 2016
Validated questionnaire [Questionnaire pack]	0.1	26 July 2016

IRAS project ID	212524

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Mr Scott Harfield
Tel: 01273696955
Email: scott.harfield@bsuh.nhs.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	A non-substantial amendment was made to the PIS and consent form (addition of IRAS ID) after REC favourable opinion.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The Statement of Activities will act as the agreement between the site and the participating NHS organisation.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			research study
4.3	Financial arrangements assessed	Yes	As detailed in the Statement of Activities no funding will be provided to sites.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is one site type in this study. All study activities will take place at site. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**.

- Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.
- The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

A PI is expected at site and these have already been identified.

Sponsor recommends that those working on the study have completed up to date GCP training.

GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

A letter of access will be required by any member of the team carrying out research activities if they do not already have a contractual relationship with the participating site in which the activities are taking place. Occupational health clearance and DBS checks should be confirmed.

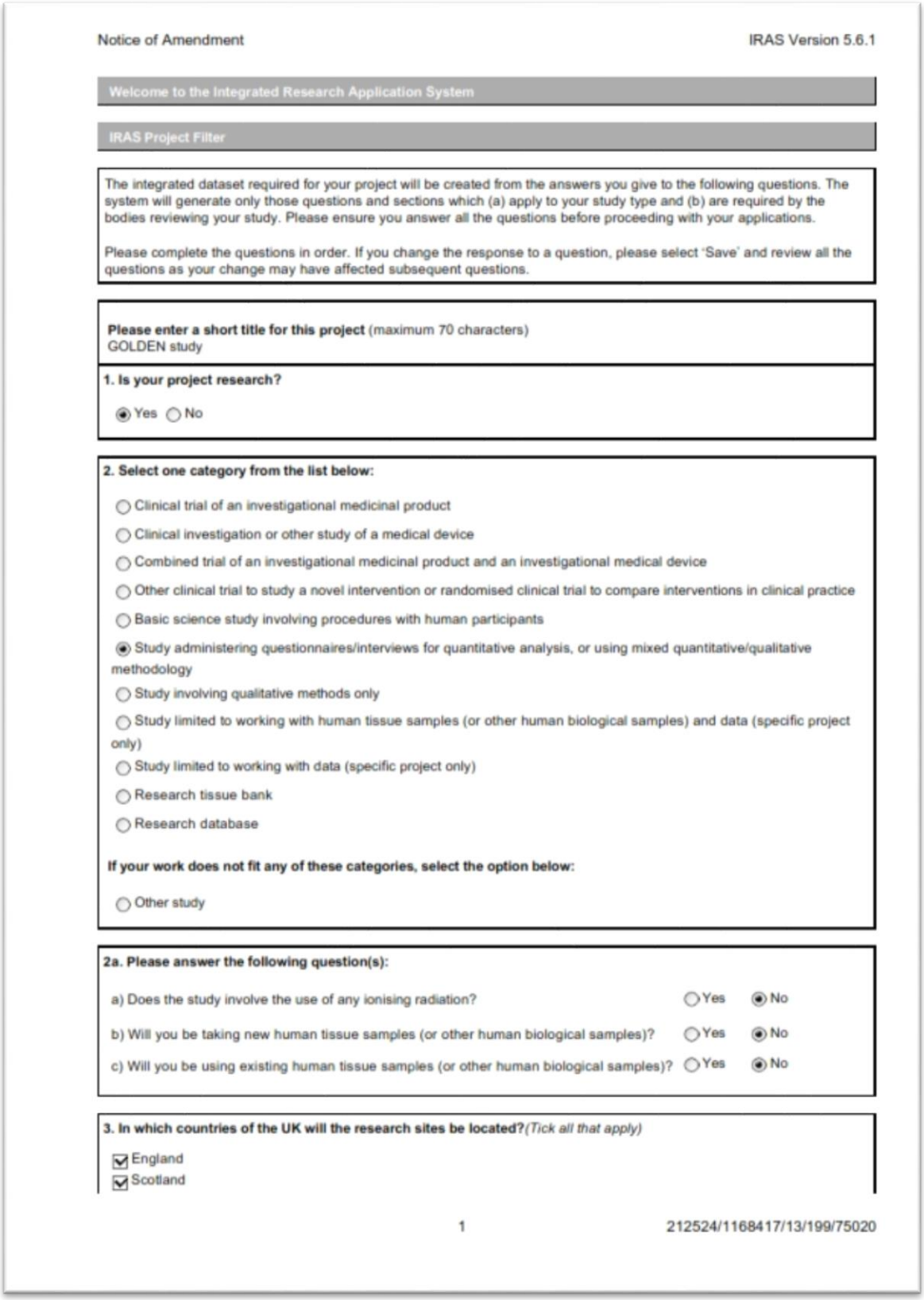
Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.

IRAS project ID	212524

The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

Figure 17: Amendment for the GOLDEN study



Notice of Amendment IRAS Version 5.6.1

Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
GOLDEN study

1. Is your project research?

◉ Yes ○ No

2. Select one category from the list below:

○ Clinical trial of an investigational medicinal product
○ Clinical investigation or other study of a medical device
○ Combined trial of an investigational medicinal product and an investigational medical device
○ Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice
○ Basic science study involving procedures with human participants
◉ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
○ Study involving qualitative methods only
○ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
○ Study limited to working with data (specific project only)
○ Research tissue bank
○ Research database

If your work does not fit any of these categories, select the option below:

○ Other study

2a. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ○ Yes ◉ No
b) Will you be taking new human tissue samples (or other human biological samples)? ○ Yes ◉ No
c) Will you be using existing human tissue samples (or other human biological samples)? ○ Yes ◉ No

3. In which countries of the UK will the research sites be located? *(Tick all that apply)*

☑ England
☑ Scotland

1 212524/1168417/13/199/75020

☐ Wales
☐ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

◉ England
○ Scotland
○ Wales
○ Northern Ireland
○ This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

☑ IRAS Form
☐ Confidentiality Advisory Group (CAG)
☐ Her Majesty's Prison and Probation Service (HMPPS)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

Most research projects require review by a REC within the UK Health Departments' Research Ethics Service. Is your study exempt from REC review?

○ Yes ◉ No

5. Will any research sites in this study be NHS organisations?

◉ Yes ○ No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

○ Yes ◉ No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

◉ Yes ○ No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

◉ Yes ○ No

Please describe briefly the involvement of the student(s):
The project is being undertaken as part of a medical doctorate degree by the Chief Investigator

9a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

◉ Yes ○ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

NOTICE OF SUBSTANTIAL AMENDMENT

Please use this form to notify the main REC of substantial amendments to all research other than clinical trials of investigational medicinal products (CTIMPs).
The form should be completed by the Chief Investigator using language comprehensible to a lay person.

Details of Chief Investigator:

	Title Forename/Initials Surname
	Dr Cressida Lorimer
Work Address	Clinical Research and Investigations Unit
	Royal Sussex Cancer Centre
	Brighton
PostCode	BN2 5BE
Email	cressida.lorimer@bsuh.nhs.uk
Telephone	01273696955
Fax	01273696955

For guidance on this section of the form refer to the guidance

Full title of study:	Geriatric assessment for OLDEr patients with glioblastoma within Neuro-oncology clinics
Lead sponsor:	Brighton and Sussex NHS Trust
Name of REC:	West Midlands - Solihull
REC reference number:	16/WM/0408

Additional reference number(s):

Ref.Number Description	Reference Number

Name of lead R&D office:	Brighton and Sussex University Hospitals NHS Trust
Date study commenced:	06.11.16
Protocol reference (if applicable), current version and date:	Protocol V0.8 02.01.2018
Amendment number and date:	Amendment number 1.0 24.01.2018

Type of amendment

(a) Amendment to information previously given in IRAS

(●) Yes ( ) No

If yes, please refer to relevant sections of IRAS in the "summary of changes" below.

(b) Amendment to the protocol

◉ Yes ○ No

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

The changes are in red text and highlighted in bold

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study

○ Yes ◉ No

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified and not approved?

○ Yes ◉ No

Summary of changes

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.
If this is a modified amendment, please explain how the modifications address the concerns raised previously by the ethics committee.
If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

As part of the analysis of the feasibility of the GOLDEN study, a questionnaire was designed for feedback from the nursing and clinical staff involved in running the study. This has a free text box however during the course of the study it has become apparent that there is much to be gained by a more detailed analysis of the experience of the clinical nurse specialists (CNS).

The CNSs have played a pivotal role in running the study and have been the most involved in day to day organisation and data collection aswell as having the most contact with the patients involved.

This analysis would be best performed by conducting a face to face semi-structured interview with each of the CNSs at The Sussex Cancer Centre, The Royal Marsden and The Beatson West of Scotland Cancer Centre. This will involve 3 interviews in all. These interviews will then be interpreted qualitatively using thematic analysis. They will be conducted by the CI.

The relevant sections of the IRAS form that are different are as follows:
A7 - the box for 'Qualitative research' should be checked
A36 - the box for 'Publication of direct quotes from respondents' should be checked
A58 - The secondary endpoint of 'impact on clinic' will now be assessed using semi structured qualitative interviews aswell as the previously mentioned questionnaires
A62 - analysis of the study will now also include qualitative interpretation using thematic analysis of the interviews

Any other relevant information

Applicants may indicate any specific issues relating to the amendment, on which the opinion of a reviewing body is sought.

List of enclosed documents

Document	*Version*	*Date*
Protocol	0.8	02/01/2018

GOLDEN CNS Interviews Topic Guide	0.1	03/01/2018
Response of Local Sponsorship Committee to amendment	0.3	24/01/2018

Declaration by Chief Investigator

1. *I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.*
2. *I consider that it would be reasonable for the proposed amendment to be implemented.*

This section was signed electronically by Dr Cressida Lorimer on 24/01/2018 11:50.

Job Title/Post:	Clinical Research Fellow
Organisation:	Brighton and Sussex NHS Trust
Email:	cressida.lorimer@bsuh.nhs.uk

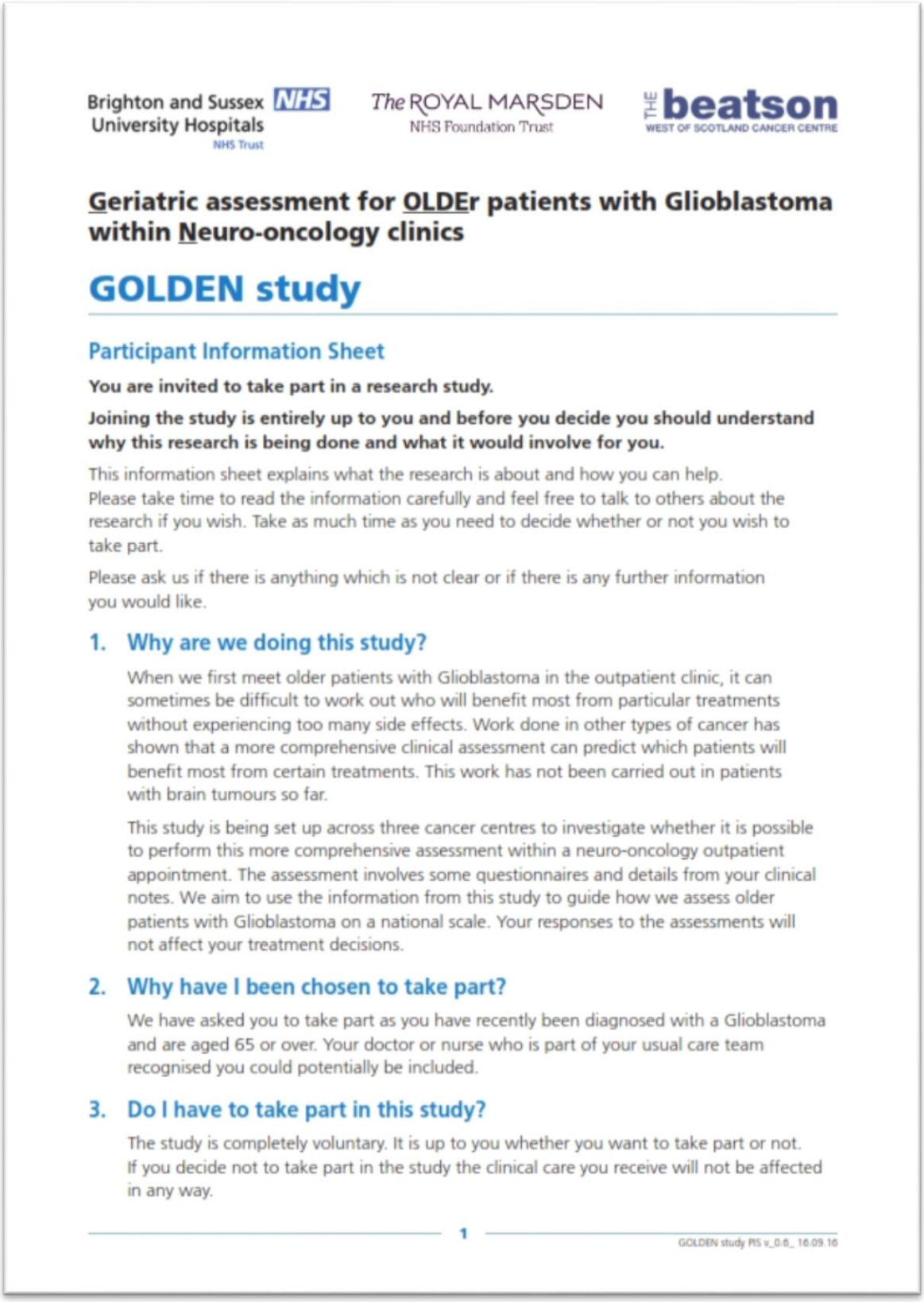
Declaration by the sponsor's representative

I confirm the sponsor's support for this substantial amendment.

This section was signed electronically by Mr Scott Harfield on 24/01/2018 11:49.

Job Title/Post:	Head of R&D
Organisation:	BSUH
Email:	scott.harfield@bsuh.nhs.uk

Figure 18: Patient Information Sheet for the GOLDEN study



Brighton and Sussex University Hospitals NHS Trust

The ROYAL MARSDEN NHS Foundation Trust

THE beatson WEST OF SCOTLAND CANCER CENTRE

Geriatric assessment for OLDEr patients with Glioblastoma within Neuro-oncology clinics

GOLDEN study

Participant Information Sheet

You are invited to take part in a research study.

Joining the study is entirely up to you and before you decide you should understand why this research is being done and what it would involve for you.

This information sheet explains what the research is about and how you can help. Please take time to read the information carefully and feel free to talk to others about the research if you wish. Take as much time as you need to decide whether or not you wish to take part.

Please ask us if there is anything which is not clear or if there is any further information you would like.

1. Why are we doing this study?

When we first meet older patients with Glioblastoma in the outpatient clinic, it can sometimes be difficult to work out who will benefit most from particular treatments without experiencing too many side effects. Work done in other types of cancer has shown that a more comprehensive clinical assessment can predict which patients will benefit most from certain treatments. This work has not been carried out in patients with brain tumours so far.

This study is being set up across three cancer centres to investigate whether it is possible to perform this more comprehensive assessment within a neuro-oncology outpatient appointment. The assessment involves some questionnaires and details from your clinical notes. We aim to use the information from this study to guide how we assess older patients with Glioblastoma on a national scale. Your responses to the assessments will not affect your treatment decisions.

2. Why have I been chosen to take part?

We have asked you to take part as you have recently been diagnosed with a Glioblastoma and are aged 65 or over. Your doctor or nurse who is part of your usual care team recognised you could potentially be included.

3. Do I have to take part in this study?

The study is completely voluntary. It is up to you whether you want to take part or not. If you decide not to take part in the study the clinical care you receive will not be affected in any way.

1

GOLDEN study PIS v_0.6_ 16.09.16

If you decide to take part you are still free to stop your participation and withdraw from the study at any time and for any reason.

4. What will happen to me if I take part?

If you decide to take part in the study your usual clinical care will not change in any way and your responses to the study assessments will not affect your treatment decisions.

If you are happy to be part of the study we would ask you to complete the enclosed consent form and bring it with you to your neuro-oncology outpatient appointment. When you come to the appointment you will be given two short questionnaires to complete in the waiting room. One of the questionnaires asks about your ability to do certain tasks around the house and the other has questions about your mood. You are welcome to ask for help from friends, family or the nursing staff for help with the questionnaires.

When you see the doctor or nurse they will then complete two more questionnaires with you as part of your appointment. These questionnaires focus on your memory, your appetite and your medications. The questionnaires have been examined to check whether they cause any distress.

Your care team will then note down some details from your hospital notes including your age and gender, any previous medical problems and the type of treatment you received. They will also ask a trial radiologist to look at your scans. They will not record anything that could identify you. If you go on to receive some treatment from the neuro oncology team they will make a note of any side effects you receive from the treatment when you see them in future appointments.

We will give you a short form with a stamped addressed envelope to take home to complete and send back to us which will ask how you found filling in the questionnaires and whether you had any feedback for the study organisers. After you have completed this your participation in the study will be finished.

5. What are the possible side effects, risks and potential harms of taking part in the study?

Participating in the study requires you to complete the questionnaires that are given to you when you attend for your hospital appointment. This may mean your appointment is 5–10 minutes longer than it would be otherwise. It does not involve any extra hospital visits, invasive tests or taking any medication. Your routine clinical care and follow up will not be affected in any way. No risks are anticipated in filling in these questionnaires however it is possible that some people may find answering the questions causes distress. If you have any concerns whilst completing the questionnaires please let us know and we can provide extra support and advice.

6. What are the possible benefits of taking part in the study?

There may be no direct benefits to you from taking part in the study. However the study will answer some important questions surrounding the issues that affect older patients with brain tumours and help us to choose between different treatment options.

7. Will I be paid for taking part in the study?

You will not be paid to take part in this study. No members of the trial team are being paid to run the study either.

8. Who will be told I am taking part in the study?

Your usual neuro-oncology care team and your GP will be aware you are taking part in the study. No one else will be told unless you choose to tell them yourselves.

9. How is my information kept confidential?

We will follow ethical and legal practice and all of your information will be kept confidential. All information that is collected about you during the study will be kept strictly confidential and will be stored in a secure manner compliant with the Data Protection Act. If you join the study, a unique study number will be used and there will be nothing to identify you in the data we store.

However, if you tell us about serious risk of harm to yourself or others we will need to break confidentiality – which means letting your GP or other teams know. We will tell you if we do this.

10. What happens if I want to leave the study?

If you join the study, you are still free to leave at any time. If you have already provided us with your completed questionnaires we would plan to keep the anonymised information. If you would prefer all anonymous information to be deleted then please let us know.

11. What happens with the results of the study?

Your identity will not appear in any report or publication. The study is being run across three cancer centres and, once completed, the anonymised results will be collected together and analysed. We will aim to present the results at medical conferences and/or publish in medical journals. We are happy to share the results of this study with you if you would like.

12. What happens if there is a problem?

BSUH hold insurance policies which apply to this study.

If you wish to complain or have any concerns about any aspect of the way you have been treated during the course of this study you should immediately inform your local neuro-oncology clinical nurse specialist (see contact details overleaf).

The normal NHS complaints procedures are also available to you. The Patient Advice and Liaison Service (PALS) can be contacted on the following numbers for advice on general matters surrounding being involved in research as well as if there are any problems:

Sussex Cancer Centre: **01273 696955 ext 4029** or via email at **complaints@bsuh.nhs.uk**

The Beatson Cancer Centre: **0141 3017000**

The Royal Marsden: **0800 7837176** or via the contact form at **www.royalmarsden.nhs.uk/contact-us/get-in-touch**

13. Who is organising and paying for the research?

The research is being organised through Brighton and Sussex University Hospitals Trust, who are the sponsor for the study. The study is supported by *brainstrust* with funding given for administrative costs.

14. What should I do if I want to take part?

If you decide to take part in the study please complete the enclosed consent form and bring it to your next neuro-oncology clinic visit. If you have any questions about taking part in the trial please do not hesitate to contact one of the trial team on the numbers below.

Contacts for further information

If you have any questions about this research, or if you have found this information sheet distressing in any way, please feel free to call:

Sussex Cancer Centre

Gill Walsh
Macmillan Neuro-oncology Clinical Nurse Specialist
Sussex Cancer Centre,
Royal Sussex County Hospital,
Eastern Road, Brighton BN2 5BE

Tel: **01273 696955 ext 4985**
Mobile: **07769 884957**
E-mail: **gill.walsh@bsuh.nhs.uk**

Dr Cressida Lorimer
Clinical Research Fellow in Neuro-Oncology
CIRU, Royal Sussex County Hospital,
Eastern Road, Brighton

Tel: **01273 696955 ext 7044**
E-mail: **cressida.lorimer@bsuh.nhs.uk**

The Royal Marsden Hospital

Alison Corbett
Macmillan Neuro-Oncology Clinical Nurse Specialist
The Royal Marsden Hospital,
Downs Road, Sutton

Tel: **0208 915 6011**
E-mail: **neuro-oncology@rmh.nhs.uk**

Katie Bedborough
Macmillan Neuro-Oncology Clinical Nurse Specialist
The Royal Marsden Hospital,
Downs Road, Sutton

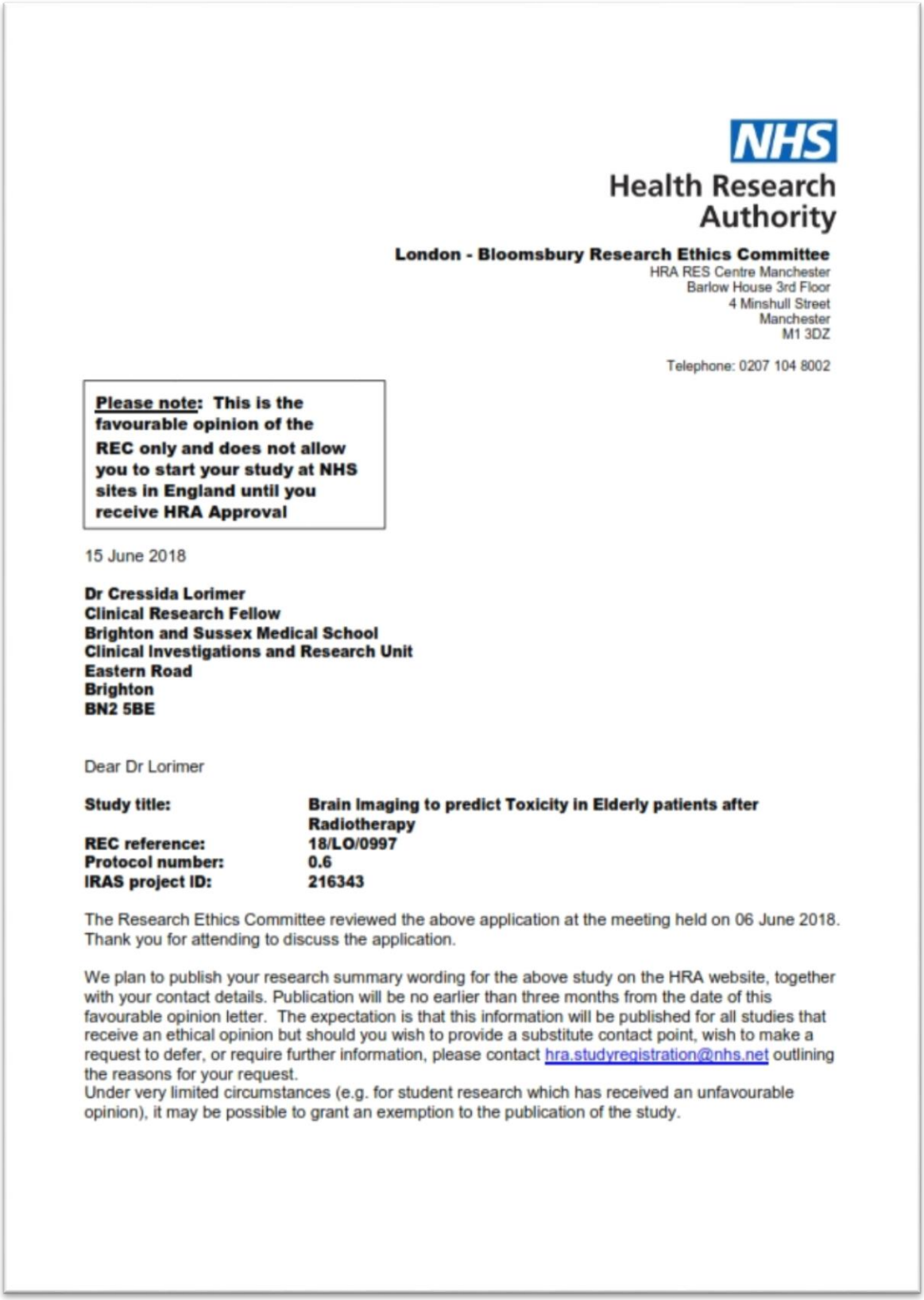
Tel: **0208 915 6011**
E-mail: **neuro-oncology@rmh.nhs.uk**

The Beatson Cancer Centre

Mairi Mackinnon
Neuro-oncology Clinical Nurse Specialist
The Beatson West of Scotland
Cancer Centre,
1053 Great Western Road,
Glasgow G12 0YN

Tel: **0141 3017602**
E-mail: **mairi.mackinnon3@ggc.scot.nhs.uk**

Figure 19: Ethical approval for the BRITER study



NHS
Health Research Authority

London - Bloomsbury Research Ethics Committee
HRA RES Centre Manchester
Barlow House 3rd Floor
4 Minshull Street
Manchester
M1 3DZ

Telephone: 0207 104 8002

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

15 June 2018

Dr Cressida Lorimer
Clinical Research Fellow
Brighton and Sussex Medical School
Clinical Investigations and Research Unit
Eastern Road
Brighton
BN2 5BE

Dear Dr Lorimer

Study title:	**Brain Imaging to predict Toxicity in Elderly patients after Radiotherapy**
REC reference:	**18/LO/0997**
Protocol number:	**0.6**
IRAS project ID:	**216343**

The Research Ethics Committee reviewed the above application at the meeting held on 06 June 2018. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request.
Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

NHS
Health Research Authority

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Suggestion Only

The Committee asked Dr Lorimer to maybe think about putting in a sentence into the Information Sheet regarding the benefit it would have for future care and treatment of this patient group.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites taking part in the study taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

Social or scientific value; scientific design and conduct of the study

The Committee congratulated Dr Cressida Lorimer on her very well written application and protocol.

The Committee wondered how Dr Lorimer envisaged this study would contribute to future treatment.

You replied that these patients were a very vulnerable group of people. There is currently no standardised way to treat this group of people. It depends on the balance of treatment and the side effects from the treatment. You went on to say that you can look at the tumour sample and decide what would work if they had chemotherapy, but that there currently wasn't a way to predict who would be more at risk of side effects and who would benefit the most from radiotherapy. You stated that they would have a conversation with patients to tell them that they may have a reduction in quality of life if they went down that route.

You would hope that you could offer the treatment to the people who would get the most benefit from it with the least side effects.

The Committee suggested that Dr Lorimer put in a sentence into the Information Sheet regarding the benefit it would have for future care and treatment of this patient group.

Recruitment arrangements and access to health information, and fair participant selection

The Committee noted that in answer to A33 of the IRAS application form it stated that friends or family could act as interpreters should the participants not understand English. The Committee was in agreement that this would not be appropriate and stated that an NHS interpreter should be used. The Committee sought further clarification as to what the likelihood would be of the researchers recruiting non-English participants into the study.

You replied that if participants could not understand English, than they would probably not be recruited to the study. You went on to say that the validated questionnaires that would be used in the study were not designed for non-English speaking people, so any non-English speaking participants would struggle with them. You stated that the trail teams would be looking at the demographics of the potential participants.

You went on to say that in a previous study conducted at the same 3 sites, Brighton and the Scottish site the majority of the participants were predominantly white, and English was their first language and that the 3rd site, the Marsden had more of a wide ethnic diverse mix of participants.

The Committee was satisfied with the response.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee noted that the side effects of the contrast dye used for the scan were not listed in the Information Sheet and queried why they were not listed.

You replied that these participants would have already had a number of MRI scans and that they would be aware of any risks as they would have had things explained to them before.

The Committee understood that this was a very sick group of people and queried whether they understood their prognosis and what their life expectancy would be.

You replied that they would be told that it is incurable and then depending on how much the patient wanted to know would determine how much the doctors tell them about their life expectancy. You replied that some patients do not want to know how long they have left. You said that the prognosis is likely to be months.

The Committee queried whether the doctors would tell the family members the prognosis if the patient did not want to know.

You replied that they would only divulge information to the family if the patient had given permission to do so.

The Committee was content with the response.

Informed consent process and the adequacy and completeness of participant information

The Committee noted that it stated in the IRAS application form that participants would be given "sufficient time" to consider the Information Sheet and whether they wished to consent to take part in the study. The Committee sought further clarification as to what was meant by "sufficient time".

You replied that normally in previous studies they usually state between 24-48 hours. You went on to state that you have not given a fixed time amount for this study; as potentially some of these participants would have a slower cognitive thought process and that you wanted to make sure that they understood the expectations of the study clearly. You went on to say that all the participants would have their capacity assessed and that the study team would go through the study with the participant and their relative or carer. You also said that they would answer questions and that the participants would be free to take the Information Sheet away for further thought before they signed the consent form.

The Committee was satisfied with the response.

Please contact the REC Manager if you feel that the above summary is not an accurate reflection of the discussion at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*

Covering letter on headed paper		08 May 2018
GP/consultant information sheets or letters [GP letter]	0.1	01 March 2018
IRAS Application Form [IRAS_Form_09052018]		09 May 2018
IRAS Checklist XML [Checklist_09052018]		09 May 2018
Letter from funder		09 May 2018
Letter from sponsor		26 April 2018
Other [PPI feedback]		
Participant consent form [Consent form]	0.1	09 January 2018
Participant information sheet (PIS) [PIS]	0.2	12 February 2018
Referee's report or other scientific critique report		08 February 2018
Research protocol or project proposal [Study protocol]	0.6	23 April 2018
Summary CV for Chief Investigator (CI) [CV]		01 March 2018
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Flowchart]	0.1	01 March 2018
Validated questionnaire [EORTC quality of life questionnaire QLQ-C30]	3	
Validated questionnaire [EORTC quality of life questionnaire elderly subset of questions QLQ-ELD14]		
Validated questionnaire [EORTC quality of life questionnaire brain subset of questions QLQ-BN20]		
Validated questionnaire [MoCA questionnaire]		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

18/LO/0997	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

On behalf of
Reverend Jim Linthicum
Chair

E-mail: nrescommittee.london-bloomsbury@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

"After ethical review – guidance for researchers"

Copy to: Mr Scott Harfield,
Brighton & Sussex University Hospitals NHS Trust

NHS
Health Research Authority

London - Bloomsbury Research Ethics Committee

Attendance at Committee meeting on 06 June 2018

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms Sally Doganis	Executive Producer and Media Consultant	Yes	
Ms Kalvinder Gahir	Practice Support Pharmacist	Yes	
Dr Paul Gorczynski **in the Chair**	Chartered Psychologist	Yes	
Mrs Sally Gordon Boyd	Medical Ethicist	No	
Professor Richard Green	Professor of Psychiatry and Lecturer in Law (retired)	Yes	
Reverend Jim Linthicum	Hospital Chaplain	No	
Ms Cathy MacLean	Clinical Project Manager	Yes	
Ms Clare Madin	Semi-Retired Clinical Data Management Manager	Yes	
Ms Michelle McPhail	Senior Lecturer in Management Studies	Yes	
Miss Chika Ozongwu	Clinical Scientist	No	
Dr Alexa Strachan	Anaesthetic Trainee	Yes	
Dr Ruth Williams	Consultant Paediatric Neurologist	No	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Ewa Grzegorska	Acting REC Manager

Figure 20: HRA approval for the BRITER study

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Cressida Lorimer
Clinical Research Fellow
Brighton and Sussex Medical School
Clinical Investigations and Research Unit
Eastern Road
Brighton
BN2 5BE

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

28 June 2018

Dear Dr Lorimer

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Brain Imaging to predict Toxicity in Elderly patients after Radiotherapy**
IRAS project ID:	**216343**
Protocol number:	**0.6**
REC reference:	**18/LO/0997**
Sponsor	**Brighton and Sussex NHS Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

Page **1** of **7**

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Mr Scott Harfield
E-mail scott.harfield@bsuh.nhs.uk
Telephone 01273696955

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **216343**. Please quote this on all correspondence.

IRAS project ID	216343

Yours sincerely

Catherine Adams
Senior Assessor
Email: hra.approval@nhs.net

Copy to: *Mr Scott Harfield, Brighton & Sussex University Hospitals NHS Trust, Sponsor's Representative*

IRAS project ID	216343

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper		08 May 2018
GP/consultant information sheets or letters [GP letter]	0.1	01 March 2018
HRA Schedule of Events [IRAS 216343_SoE]	1	12 June 2018
HRA Statement of Activities	2	28 June 2018
IRAS Application Form [IRAS_Form_09052018]		09 May 2018
Letter from funder		09 May 2018
Letter from sponsor		26 April 2018
Other [PPI feedback]		
Participant consent form [Consent form]	0.1	09 January 2018
Participant information sheet (PIS)	0.3	26 June 2018
Referee's report or other scientific critique report		08 February 2018
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Validated questionnaire [EORTC quality of life questionnaire brain subset of questions QLQ-BN20]		
Validated questionnaire [MoCA questionnaire]		

IRAS project ID	216343

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	The Information sheet has been updated to comply with GDPR requirements.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The statement of activities will act as agreement of an NHS organisation to participate. The sponsor is not requesting and does not expect any other site agreement.
4.2	Insurance/indemnity arrangements assessed	Yes	No comments
4.3	Financial arrangements assessed	Yes	Details of funding available and the means to recoup are detailed in the statement of activities.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments

IRAS project ID	216343

Section	Assessment Criteria	Compliant with Standards	Comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
All organisations will be undertaking the same activity (i.e. there is only one 'site-type') as detailed in the protocol and supporting documentation. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Local Principal Investigator is required for this type of study, and has been identified at the participating NHS site. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

IRAS project ID	216343

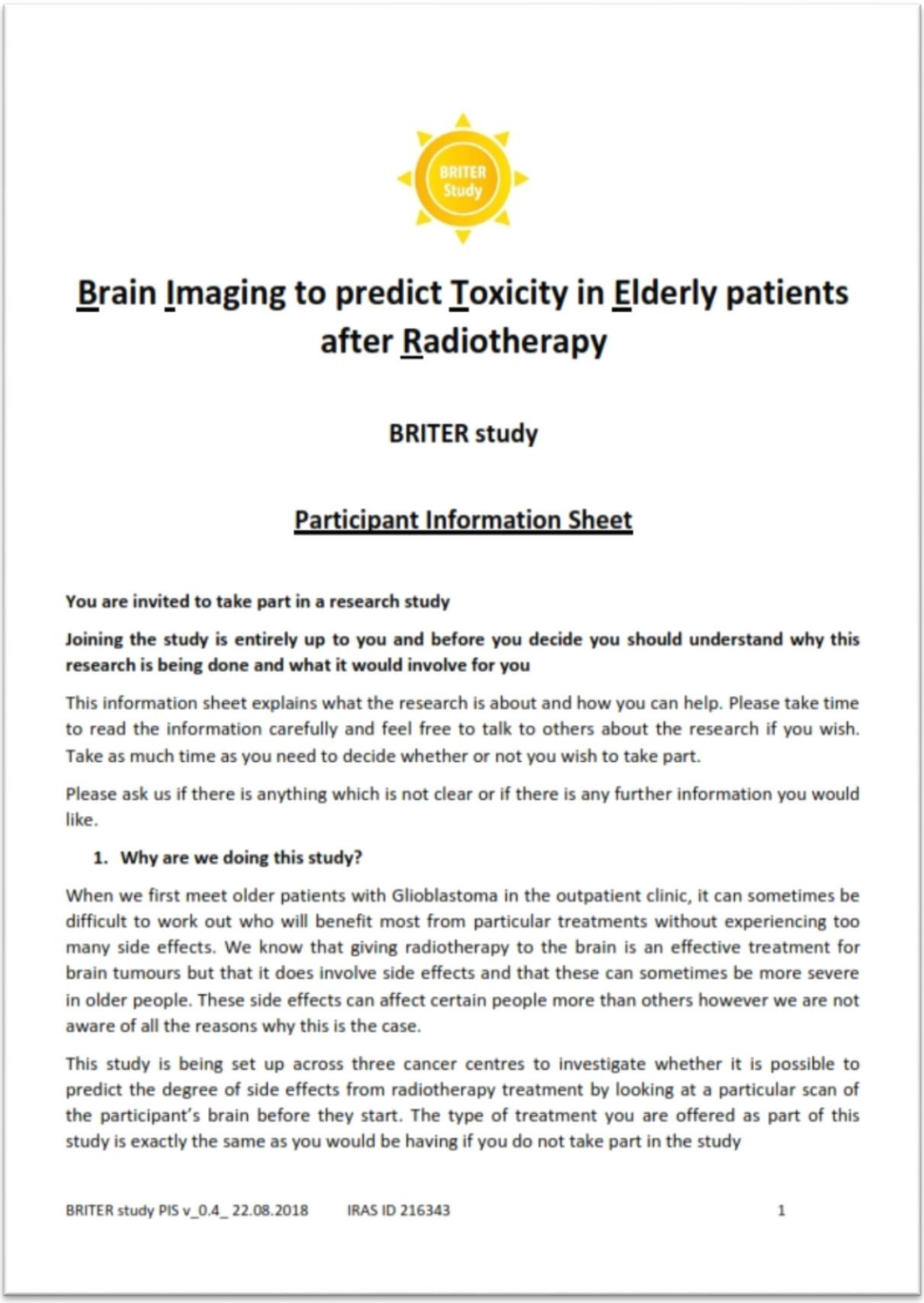
HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
All research activities at sites will be undertaken by local staff, it is therefore unlikely that additional arrangements (letters of access or honorary research contracts) will be applicable, except where individuals employed by another Trust or University (e.g. local network staff) are involved, and arrangements are not already in place. Where arrangements are not already in place, Researchers undertaking the research activities listed in A18 and A19 of the IRAS form would be expected to obtain an honorary research contract from one NHS organisation (if university Researcher), followed by Letters of Access for subsequent organisations or an NHS to NHS confirmation of pre-engagement checks letter, if NHS employed. This would be on the basis of a Research Passport and should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking administration of questionnaires only would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales to aid study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

Figure 21: Patient Information Sheet for the BRITER study



Brain Imaging to predict Toxicity in Elderly patients after Radiotherapy

BRITER study

Participant Information Sheet

You are invited to take part in a research study

Joining the study is entirely up to you and before you decide you should understand why this research is being done and what it would involve for you

This information sheet explains what the research is about and how you can help. Please take time to read the information carefully and feel free to talk to others about the research if you wish. Take as much time as you need to decide whether or not you wish to take part.

Please ask us if there is anything which is not clear or if there is any further information you would like.

1. **Why are we doing this study?**

When we first meet older patients with Glioblastoma in the outpatient clinic, it can sometimes be difficult to work out who will benefit most from particular treatments without experiencing too many side effects. We know that giving radiotherapy to the brain is an effective treatment for brain tumours but that it does involve side effects and that these can sometimes be more severe in older people. These side effects can affect certain people more than others however we are not aware of all the reasons why this is the case.

This study is being set up across three cancer centres to investigate whether it is possible to predict the degree of side effects from radiotherapy treatment by looking at a particular scan of the participant's brain before they start. The type of treatment you are offered as part of this study is exactly the same as you would be having if you do not take part in the study

BRITER study PIS v_0.4_ 22.08.2018 IRAS ID 216343 1

2. Why have I been chosen to take part?

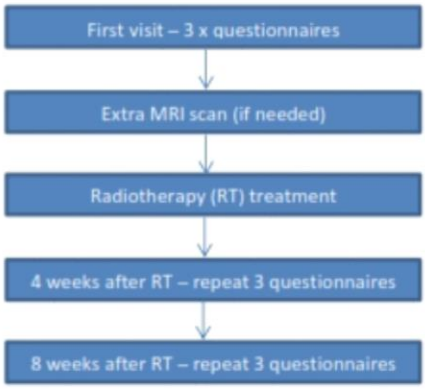
We have asked you to take part as you have recently been diagnosed with a Glioblastoma, are aged 65 or over, are able to have an MRI scan and have been offered radiotherapy to the brain as part of your treatment. Your doctor or nurse who is part of your usual care team recognised you could potentially be included.

3. Do I have to take part in this study?

The study is completely voluntary. It is up to you whether you want to take part or not. If you decide not to take part in the study the clinical care you receive will not be affected in any way. If you decide to take part you are still free to stop your participation and withdraw from the study at any time and for any reason.

4. What will happen to me if I take part?

If you decide to take part in the study the following flowchart explains the process.



The questionnaires are designed to assess how you manage at the moment, your mood and your quality of life. You are welcome to ask for help from friends, family or the nursing staff for help with the questionnaires. Your treatment plan will not be affected in any way and your responses to the study assessments will not affect your treatment decisions. If you are happy to be part of the study we would ask you to complete the enclosed consent form.

Your care team will also note down some details from your hospital notes including your age and gender, any previous medical problems and the type of treatment you have received. They will not record anything that could identify you.

As part of the study we need to look at the MRI scans you had during you diagnosis. Occasionally we may need to perform another MRI scan before you start your radiotherapy treatment. This may involve travelling to another site to have your scan performed. The scan will involve the same process as the MRI scan you had during your diagnosis but may take 5-10 minutes longer as we take some extra pictures. It may involve the use of a contrast dye which is administered through a small cannula into a vein in your arm during the scan.

5. What are the possible side effects, risks and potential harms of taking part in the study?

Participating in the study requires you to complete the questionnaires that are given to you when you attend for your hospital appointments. This may mean your appointments are 5-10 minutes longer than they would be otherwise. It also may involve an extra MRI scan with the contrast dye. This is the same process as the MRI scan you had as part of your diagnosis. Further details would be given to you prior to the scan.

Your routine clinical care and follow up will not be affected in any way. No risks are anticipated in filling in these questionnaires however it is possible that some people may find answering the questions causes distress. If you have any concerns whilst completing the questionnaires please let us know and we can provide extra support and advice.

6. What are the possible benefits of taking part in the study?

There may be no direct benefits to you from taking part in the study. However the study will help to answer some important questions surrounding the issues that affect older patients with brain tumours and help us to choose between different treatment options in the future.

7. Will I be paid for taking part in the study?

You will not be paid to take part in this study however the study team will cover travel expenses if you need to go to a different site to have your MRI scan. No members of the study team are being paid to run the study.

8. Who will be told I am taking part in the study?

Your usual neuro-oncology care team and your GP will be aware you are taking part in the study. No one else will be told unless you choose to tell them yourselves.

9. How is my information kept confidential?

We will follow ethical and legal practice and all of your information will be kept confidential. All information that is collected about you during the study will be kept strictly confidential and will be stored in a secure manner compliant with the Data Protection Act. If you join the study, a unique study number will be used and there will be nothing to identify you in the data we store.

However, if you tell us about serious risk of harm to yourself or others we will need to break confidentiality - which means letting your GP or other teams know. We will tell you if we do this.

Brighton and Sussex University Hospitals Trust (BSUH) is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. BSUH will keep identifiable information about you for less than 3 months after the end of the study.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information by e-mailing sponsorship.approvals@bsuh.nhs.uk.

Your local oncology centre will collect information from you and your medical records for this research study in accordance with HRA instructions.

Your local oncology centre will keep your name, NHS number and contact details confidential and will not pass this information to BSUH. Your local oncology centre will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from BSUH and regulatory organisations may look at your medical and research records to check the accuracy of the research study. BSUH will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

Your local oncology centre will keep identifiable information about you from this study for 5 years after the study has finished.

BSUH will collect information about you for this research study from your treating oncology centre. Your treating oncology centre will not provide any identifying information about you to BSUH. We will use this information to try to answer the research question outlined in Section 1.

10. What happens if I want to leave the study?

If you join the study, you are still free to leave at any time. If you have already had your MRI and provided us with your completed questionnaires we would plan to keep the anonymised information. If you would prefer all anonymous information to be deleted then please let us know.

11. What happens with the results of the study?

Your identity will not appear in any report or publication. The study is being run across three cancer centres and, once completed, the anonymised results will be collected together and analysed. We will aim to present the results at medical conferences and/or publish in medical journals. We are happy to share the results of this study with you if you would like.

12. What happens if there is a problem?

If you have any concerns about any aspect of the way you have been treated during the course of this study you should immediately inform your local neuro-oncology clinical nurse specialist (see contact details overleaf).

The normal NHS complaints procedures are also available to you. The Patient Advice and Liaison Service (PALS) can be contacted on the following numbers for advice on general matters surrounding being involved in research aswell as if there are any problems.

13. Who is organising and paying for the research?

The research is being organised through Brighton and Sussex University Hospitals Trust, who are the sponsor for the study. The study is supported by The Sussex Cancer Fund and The Brains Trust.

14. What should I do if I want to take part?

If you decide to take part in the study please complete the enclosed consent form. If you have any questions about taking part in the study please do not hesitate to contact one of the study team on the numbers below.

Contacts for further information

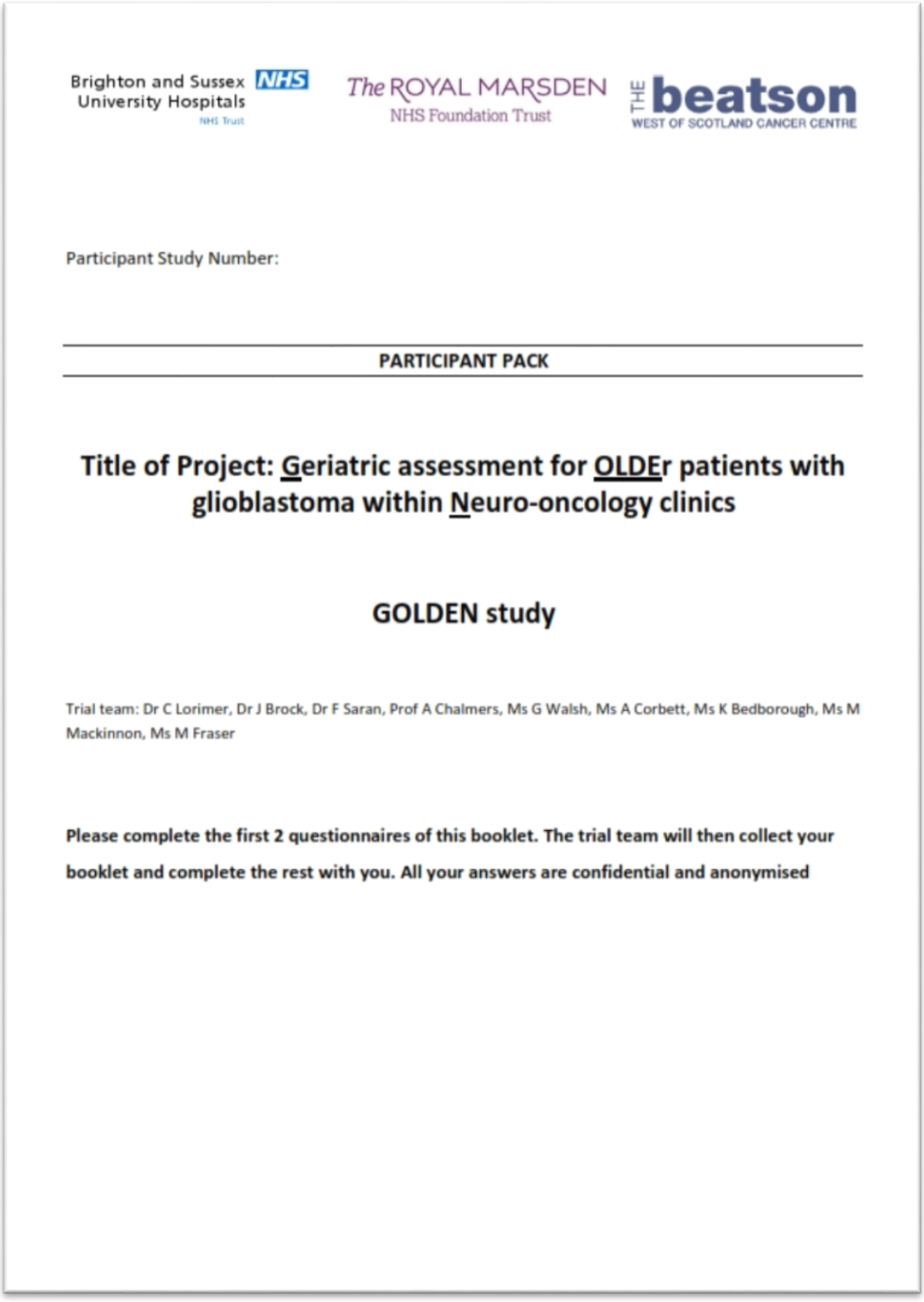
If you have any questions about this research, or if you have found this information sheet distressing in any way, please feel free to call:

Please insert local centre	
PLEASE INSERT LOCAL CONTACT DETAILS HERE	

Thank you

Chapter 9 Appendix 2: CRFs, Questionnaires and Topic Guide

Figure 22: GOLDEN study CRF



Brighton and Sussex University Hospitals NHS Trust

The ROYAL MARSDEN NHS Foundation Trust

THE beatson WEST OF SCOTLAND CANCER CENTRE

Participant Study Number:

PARTICIPANT PACK

Title of Project: Geriatric assessment for OLDEr patients with glioblastoma within Neuro-oncology clinics

GOLDEN study

Trial team: Dr C Lorimer, Dr J Brock, Dr F Saran, Prof A Chalmers, Ms G Walsh, Ms A Corbett, Ms K Bedborough, Ms M Mackinnon, Ms M Fraser

Please complete the first 2 questionnaires of this booklet. The trial team will then collect your booklet and complete the rest with you. All your answers are confidential and anonymised

1. IADLs

Please complete the following questionnaire with a friend, family member or member of the trial team.

Tick the box next to the reply that most accurately describes what you have been able to do in the last week:

Activity	Tick	Activity	Tick
Ability to use telephone		**Laundry**	
Operates telephone on own initiative looks up and dials numbers, etc.		Does personal laundry completely	
Dials a few well-known numbers		Launders small items; rinses stockings, etc.	
Answers telephone but does not dial		All laundry must be done by others	
Does not use telephone at all			
Shopping		**Mode of transportation**	
Takes care of all shopping needs independently		Travels independently on public transportation or drives own car	
Shops independently for small purchases		Arranges own travel via taxi, but does not otherwise use public transportation	
Needs to be accompanied on any shopping trip		Travels on public transportation when assisted or accompanied by another	
Unable to shop		Travel limited to taxi or automobile with assistance of another	
		Does not travel at all	
Food preparation		**Responsibility for own medications**	
Plans, prepares, and serves adequate meals independently		Is responsible for taking medication in correct dosages at correct time	
Prepares adequate meals if supplied with ingredients		Takes responsibility if medication is prepared in advance in separate dosages	
Heats and serves prepared meals, or prepares meals but does not maintain adequate diet		Is not able to dispense own medication	
Needs to have meals prepared and served			
Housekeeping		**Ability to handle finances**	
Maintains house alone or with occasional assistance (e.g., "heavy work domestic help")		Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects and keeps track of income	
Performs light daily tasks such as dishwashing, bed making		Manages day-to-day purchases, but needs help with banking, major purchases, etc.	
Performs light daily tasks but cannot maintain acceptable level of cleanliness alone		Incapable of handling money	
Needs help with all home maintenance tasks			
Does not participate in any housekeeping tasks			

2. HADS

Please complete the following questionnaire on your own if possible. Tick the box beside the reply that is closest to how you have been feeling in the past week. Don't take too long over your replies: **your immediate is best**

	Tick		Tick
I feel tense or 'wound up':		**I feel as if I am slowed down:**	
Most of the time		Nearly all the time	
A lot of the time		Very often	
From time to time, occasionally		Sometimes	
Not at all		Not at all	
I still enjoy the things I used to enjoy:		**I get a sort of frightened feeling like 'butterflies' in the stomach:**	
Definitely as much		Not at all	
Not quite so much		Occasionally	
Only a little		Quite Often	
Hardly at all		Very Often	
I get a sort of frightened feeling as if something awful is about to happen:		**I have lost interest in my appearance:**	
Very definitely and quite badly		Definitely	
Yes, but not too badly		I don't take as much care as I should	
A little, but it doesn't worry me		I may not take quite as much care	
Not at all		I take just as much care as ever	
I can laugh and see the funny side of things:		**I feel restless as I have to be on the move:**	
As much as I always could		Very much indeed	
Not quite so much now		Quite a lot	
Definitely not so much now		Not very much	
Not at all		Not at all	
Worrying thoughts go through my mind:		**I look forward with enjoyment to things:**	
A great deal of the time		As much as I ever did	
A lot of the time		Rather less than I used to	
From time to time, but not too often		Definitely less than I used to	
Only occasionally		Hardly at all	
I feel cheerful:		**I get sudden feelings of panic:**	
Not at all		Very often indeed	
Not often		Quite often	
Sometimes		Not very often	
Most of the time		Not at all	
I can sit at ease and feel relaxed:		**I can enjoy a good book or radio or TV program:**	
Definitely		Often	
Usually		Sometimes	
Not Often		Not often	
Not at all		Very seldom	

The trial team will now complete the following questionnaires with you in your clinic appointment. Please do not fill in any further answers at this point.

3. G8 questionnaire

Items	Possible response	Tick
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?	0 = severe decrease in food intake	
	1 = moderate decrease in food intake	
	2 = no decrease in food intake	
Weight loss during last 3 months?	0 = weight loss > 3kg	
	1 = does not know	
	2 = weight loss between 1 and 3 kgs	
	3 = no weight loss	
Mobility?	0 = bed or chair bound	
	1 = able to get out of bed/chair but does not go out	
	2 = goes out	
Neuropsychological problems?	0 = severe dementia or depression	
	1 = mild dementia	
	2 = no psychological problems	
BMI? (weight in kg)/(height in m^2)	0 = BMI < 19	
	1 = BMI 19 to < 21	
	2 = BMI 21 to < 23	
	3 = BMI ≥ 23	
Takes more than 3 prescription drugs per day?	0 = yes	
	1 = no	
In comparison with other people of the same age, how does the patient consider his/her health status (pre cancer diagnosis)?	0 = not as good	
	0.5 = does not know	
	1 = as good	
	2 = better	
Age	0 = > 85	
	1 = 80-85	
	2 = < 80	
Total score		

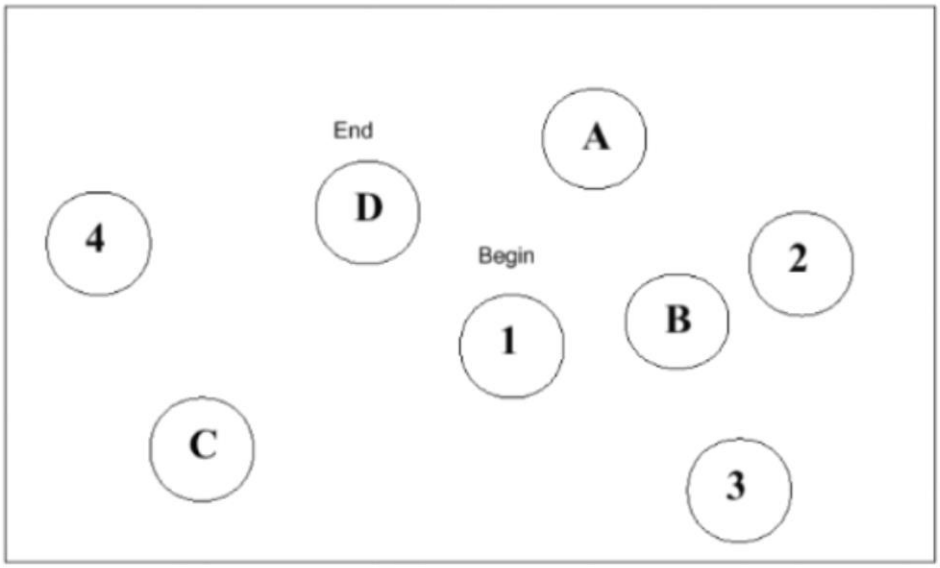
4. Trail Making Test B

The participant should be instructed to connect the circles as quickly as possible, drawing lines to connect the circles in an ascending pattern, alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.)

The participant should connect the circles without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed after five minutes have elapsed.

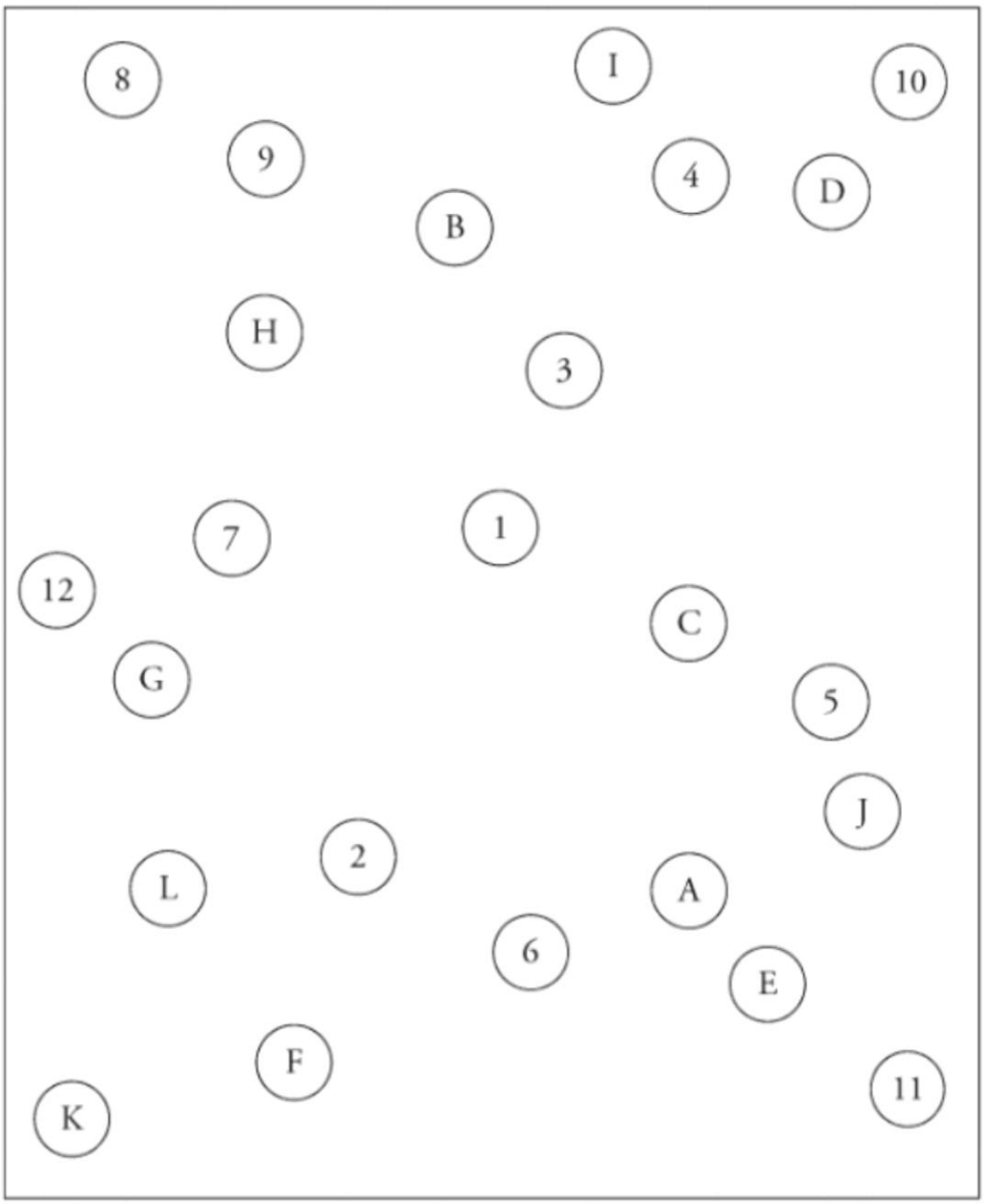
- Step 1: Demonstrate the test to the patient using the sample box below
- Step 2: Time the patient as he or she follows the "trail" made by the numbers on the test.
- Step 3: Record the time.

Sample test



PARTICIPANT NUMBER ..... Date..... GOLDEN participant pack v_0.1_26.07.16

Trail Making Test B – participant test

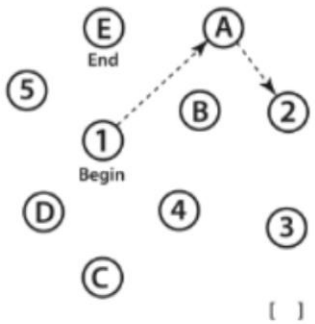


Participant time to complete (seconds).....

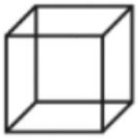
7

5. Montreal Cognitive Assessment

VISUOSPATIAL / EXECUTIVE



Copy cube



[ ] [ ]

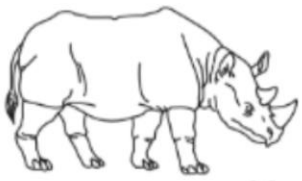
Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

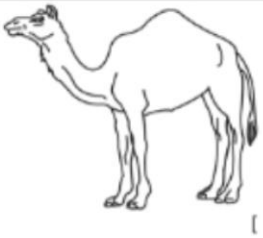
POINTS __/5

NAMING

[ ]



[ ]



[ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

 www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

8

6. Clinical details from notes

These should be completed by a member of the trial team either as part of the clinic visit by the patient or after the patient has left.

a. Date of birth:

☐☐☐☐☐☐

b. Gender:

M ☐ F ☐

c. Date of diagnosis (first imaging modality reviewed by a neuroradiology consultant within the MDM setting which shows changes consistent with a GBM):

☐☐☐☐☐☐

d. Surgery received:

Surgery	Tick	Date
None		N/A
Biopsy		
Partial debulking		
Macroscopic resection		
Other		

e. ECOG performance status

Score	Tick
0 (asymptomatic)	
1 (symptomatic but completely ambulatory)	
2 (symptomatic, <50% in bed during the day)	
3 (symptomatic, >50% in bed, but not bedbound)	
4 (bedbound)	

f. Comorbidities (please list below)

g. Charlson comorbidity index

Myocardial infarction		Diabetes	
Congestive heart failure		Diabetes with end organ damage*	
Peripheral vascular disease		Renal disease	
Stroke or TIA		Mild liver disease**	
Hemiplegia		Severe liver disease***	
COPD/asthma/bronchitis		Gastric/peptic ulcers	
Rheumatic/connective tissue disease		Cancer (excluding GBM or non-melanoma skin cancer)	
HIV or AIDS		Metastatic cancer	
Dementia/Alzheimers			

* Nephropathy, neuropathy or retinopathy
** Chronic hepatitis B/C or cirrhosis but no portal hypertension
***As above but with portal hypertension/ascites/bleeding/jaundice

h. Current medications (please list below)

i. Social situation

Situation	Tick	
Lives alone		Details of care
Lives with partner		
Lives with family		
Lives with friend		
Other		
Care package		

j. Mobility

Situation	Tick	
Independent		Details of mobility
1 x stick		
2 x stick		
Frame		
Wheelchair		
Other		

If the participant is receiving best supportive care please now file and store this booklet in a secure location for the end of the trial period

If the participant is receiving active oncological treatment please complete the following pages to document toxicity during their subsequent visits (extra pages can be printed/photocopied and added to the booklet as required)

Treatment regime:

Date of assessment

☐☐☐☐☐☐

Chemotherapy	Start date	Cycle number at this visit	Day number at this visit	Finish date
Concurrent TMZ				
Single agent TMZ				
PCV				
CCNU				
Other				

Details of 'other' treatment

.....

.....

.....

Line of treatment (please circle) 1st 2nd 3rd 4th

Performance status (please circle) 1 2 3 4

Clinical evaluation (please circle) 1 = improved 2 = stable 3 = deteriorated

Neurological status (please circle) 1 = improved 2 = stable 3 = deteriorated

Toxicities

	G0	G1	G2	G3	G4
Haematological					
Nausea					
Vomiting					
Constipation					
Rash					
Fatigue					
Seizures					
Concern re: progression					
Change in steroid use	↑		↓		
Other (eg neurological deterioration)					

Date of assessment

☐☐☐☐☐☐

Radiotherapy	Start date	Fraction number at this visit	Finish date
60Gy in 30#			
40Gy in 15#			
30Gy in 6#			
Other			

Details of 'other' treatment

.....

.....

.....

Line of treatment (please circle) 1st 2nd 3rd 4th as above

Performance status (please circle) 1 2 3 4 as above

Clinical evaluation (please circle) 1 = improved 2 = stable 3 = deteriorated as above

Neurological status (please circle) 1 = improved 2 = stable 3 = deteriorated as above

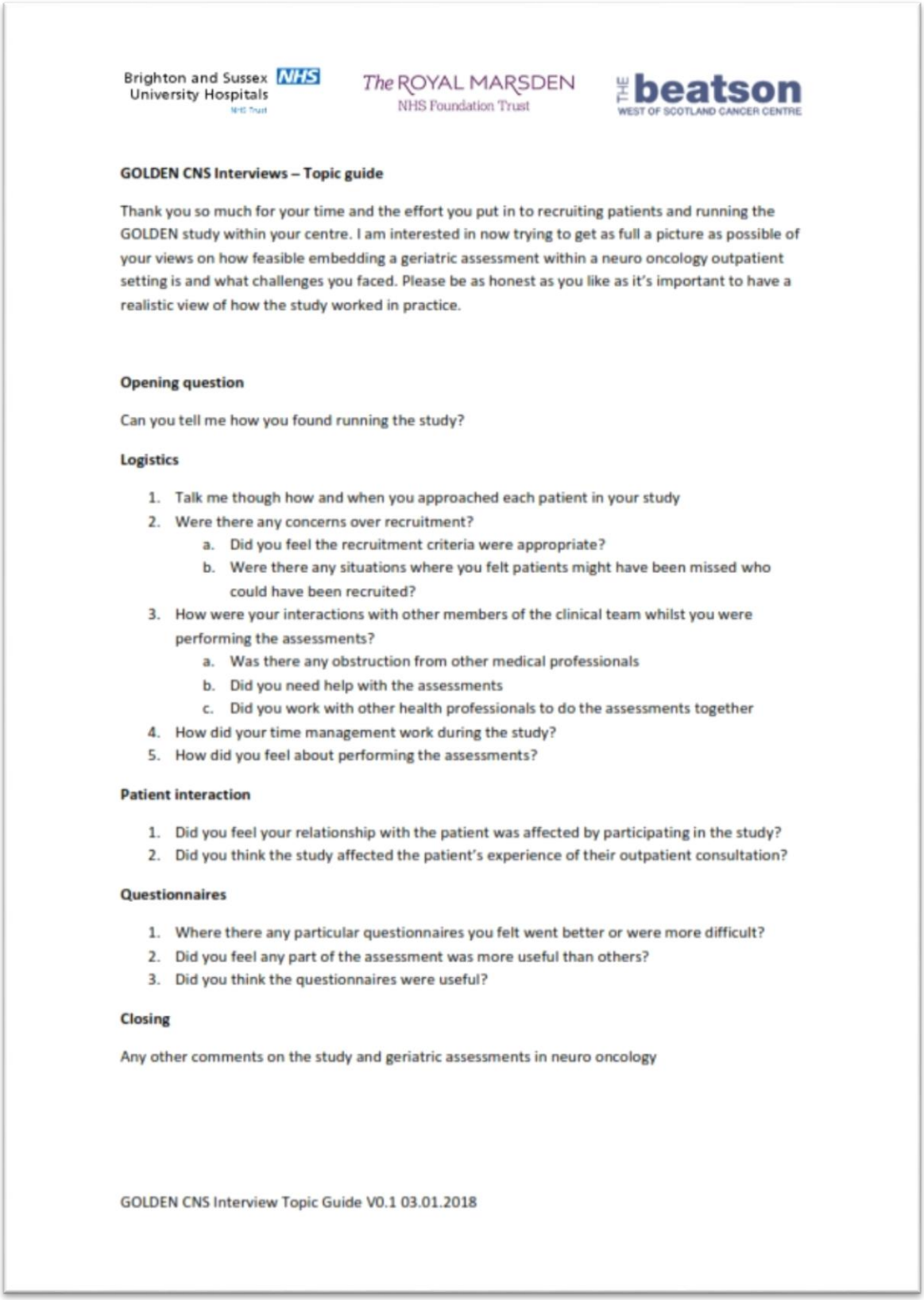
Toxicities

	G0	G1	G2	G3	G4
Fatigue					
Headache					
Nausea					
Vomiting					
Seizures					
Confusion					
Concern re: progression					
Change in steroid use	↑		↓		
Other (eg neurological deterioration)					

Toxicity grading

	CTC G0	CTC G1	CTC G2	CTC G3	CTC G4
Hb	Normal	normal - 100	80 - 100	65 - < 80	< 65
Platelets	Normal	normal – 75	≥ 50 - < 75	≥ 10 - < 50	< 10
Neutrophils	Normal	≥ 1.5 - < 2	≥ 1 - < 1.5	≥ 0.5 - < 1	< 0.5
Lymphocytes	Normal	normal – 1	≥ 0.5 - < 1	< 0.5	-
Fatigue	None	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or Lansky) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or Lansky) or loss of ability to perform some activities	bedridden or disabling
Nausea	None	able to eat	oral intake significantly decreased	no significant intake	-
Vomiting	None	1 episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	> 10 episodes in 24 hours or requiring parenteral support
Constipation	None	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Rash	None	Macular/papular eruption or erythema without symptoms	Scattered macular or papular eruption or erythema with pruritis or other associated symptoms	Generalized symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
Headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-
Seizures	None	Brief partial, no loss of consciousness	Brief generalised	Multiple seizures despite medication	Life-threatening; prolonged; repetitive
Confusion	None	Mild, not interrupting work/life performance	Moderate, interrupting work/life performance but able to function independently	Severe, significant impairment of work/life/daily living	-

Figure 23: GOLDEN Study topic guide



Brighton and Sussex University Hospitals NHS

The ROYAL MARSDEN NHS Foundation Trust

THE beatson WEST OF SCOTLAND CANCER CENTRE

GOLDEN CNS Interviews – Topic guide

Thank you so much for your time and the effort you put in to recruiting patients and running the GOLDEN study within your centre. I am interested in now trying to get as full a picture as possible of your views on how feasible embedding a geriatric assessment within a neuro oncology outpatient setting is and what challenges you faced. Please be as honest as you like as it's important to have a realistic view of how the study worked in practice.

Opening question

Can you tell me how you found running the study?

Logistics

1. Talk me though how and when you approached each patient in your study
2. Were there any concerns over recruitment?
    a. Did you feel the recruitment criteria were appropriate?
    b. Were there any situations where you felt patients might have been missed who could have been recruited?
3. How were your interactions with other members of the clinical team whilst you were performing the assessments?
    a. Was there any obstruction from other medical professionals
    b. Did you need help with the assessments
    c. Did you work with other health professionals to do the assessments together
4. How did your time management work during the study?
5. How did you feel about performing the assessments?

Patient interaction

1. Did you feel your relationship with the patient was affected by participating in the study?
2. Did you think the study affected the patient's experience of their outpatient consultation?

Questionnaires

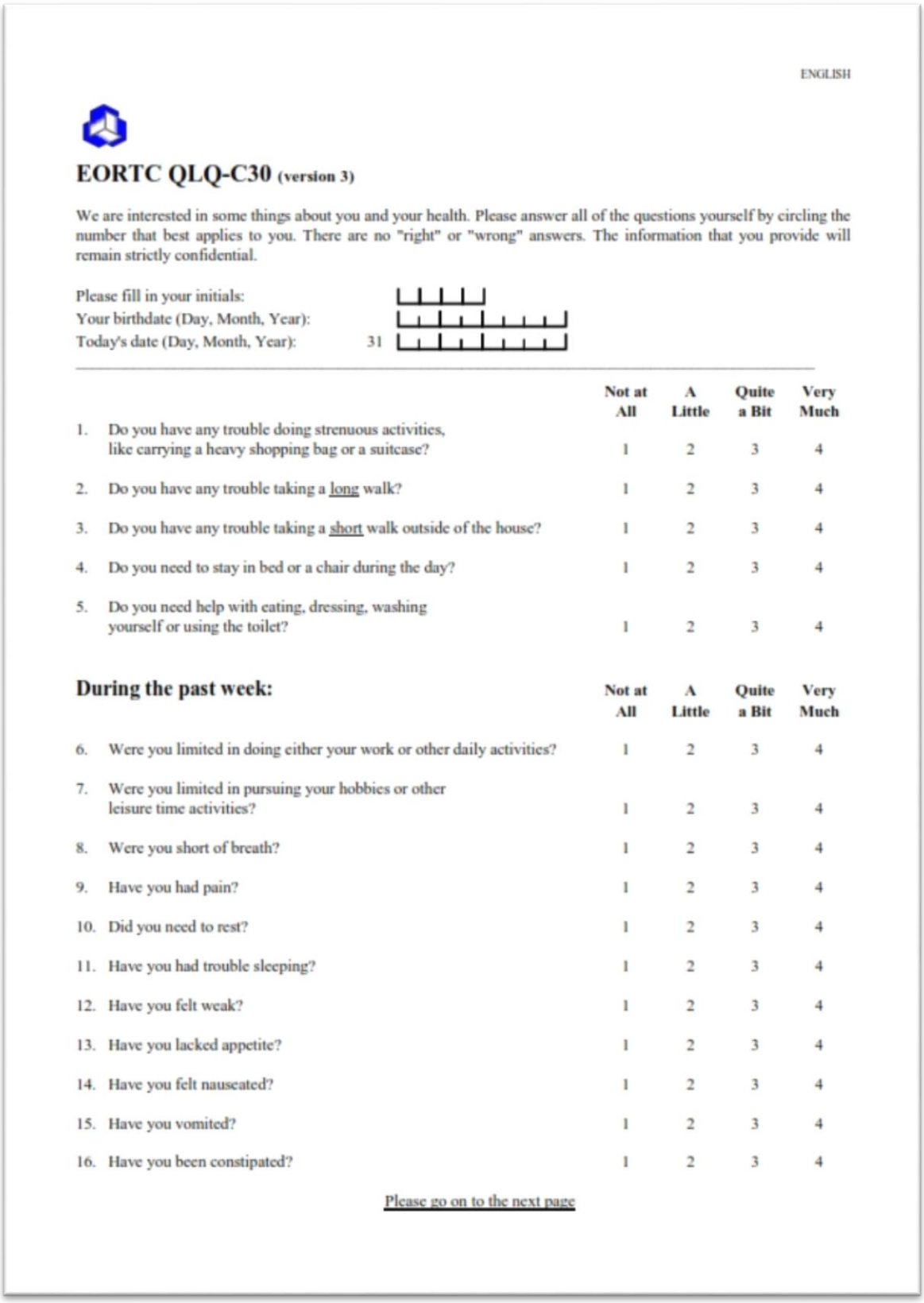
1. Where there any particular questionnaires you felt went better or were more difficult?
2. Did you feel any part of the assessment was more useful than others?
3. Did you think the questionnaires were useful?

Closing

Any other comments on the study and geriatric assessments in neuro oncology

GOLDEN CNS Interview Topic Guide V0.1 03.01.2018

Figure 24: EORTC QLQ C30 V3, BN20 and ELD14 questionnaires



ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

EORTC QLQ-ELD14

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31. Have you had difficulty with steps or stairs?	1	2	3	4
32. Have you had trouble with your joints (e.g. stiffness, pain)?	1	2	3	4
33. Did you feel unsteady on your feet?	1	2	3	4
34. Did you need help with household chores such as cleaning or shopping?	1	2	3	4
35. Have you felt able to talk to your family about your illness?	1	2	3	4
36. Have you worried about your family coping with your illness and treatment?	1	2	3	4
37. Have you worried about the future of people who are important to you?	1	2	3	4
38. Were you worried about your future health?	1	2	3	4
39. Did you feel uncertain about the future?	1	2	3	4
40. Have you worried about what might happen towards the end of your life?	1	2	3	4
41. Have you had a positive outlook on life in the last week?	1	2	3	4
42. Have you felt motivated to continue with your normal hobbies and activities?	1	2	3	4
43. How much has your illness been a burden to you?	1	2	3	4
44. How much has your treatment been a burden to you?	1	2	3	4

Chapter 10 Appendix 3: Published Chapters

Figure 25: Chapter 2 as published in Clinical Oncology

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Original Article

Challenges to Treating Older Glioblastoma Patients: the Influence of Clinical and Tumour Characteristics on Survival Outcomes

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Abstract

Aims: There is now evidence to support giving single-agent chemotherapy, radiotherapy or hypofractionated concurrent chemoradiotherapy to older patients with glioblastoma (GBM). However, the clinical basis on which treatment decisions are made is under-researched and not standardised. This retrospective, multicentre study assessed whether pre-morbid characteristics or tumour imaging features could predict for overall survival in a cohort of older patients with GBM.

Materials and methods: Patients aged > 70 years, diagnosed with GBM at three neuro-oncology centres from 2010 to 2015 were retrospectively analysed. Demographic, clinical, radiological and treatment details were included in a multivariate model to examine for predictors of overall survival.

Results: In total, 339 patients were included with a median overall survival of 3.8 months. One and 2 year overall survivalrates were 13% and 4% respectively. The median age at diagnosis was 75 years. Pre-treatment characteristics predicting for overall survival included Eastern Cooperative Oncology Group performance status over 0 (performance status 1, hazard ratio 1.66, P ¼ 0.042; performance status 2, hazard ratio 1.78, P ¼ 0.031; performance status 3, hazard ratio 2.20, P ¼ 0.008; performance status 4, hazard ratio 2.40, P ¼ 0.021), radiological evidence of mass effect (hazard ratio 1.31, P ¼ 0.049), multifocal tumours (hazard ratio 3.419, P ¼ 0.013), presenting with seizures (hazard ratio 0.63, P ¼ 0.008) and tumours confined to the cerebral hemisphere (hazard ratio 0.59, P ¼ 0.048). Subtotal resection decreased risk of death by 37% (P ¼ 0.019) and total tumour resection by 44% (P ¼ 0.019). Palliativeradiotherapy decreased risk of death by 41% (P ¼ 0.005), temozolomide alone by 60% (P ¼ 0.004) and radical chemoradiotherapy by 81% (P < 0.001).

Conclusion: Clinical presentation, performance status and imaging characteristics are independent prognostic indicators of overall survival in older GBM patients, irrespective of age or treatment received.

Key words: Glioblastoma; imaging; older; survival; treatment

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumour among the adult population, making up 46% of all malignant brain and central nervous system tumours and 15% of all primary brain tumours [1]. Incidence rates in the UK are around 4.6/100 000/year, which equates to about 2000 cases per year. Incidence peaks between the ages of 65 and 75 years, with the average age at diagnosis being 64 years. Rates in older people are increasing, with a doubling in incidence in the over 65s between the 1970s and 1990s [2]. As our global population ages it is expected that this trend will continue. The median life expectancy for GBM is in the range of 12e15 months, dropping to 3e5 months in older patients [3]. Reasons are probably multi- factorial, including aggressive tumour biology, under- treatment and comorbidities and frailty reducing treat- ment tolerance.

The standard treatment for those aged under 70 years is based on the landmark European Organization for Research and Treatment of Cancer (EORTC) trial that randomised patients to radical radiotherapy (60 Gy in 30 fractions) alone or with concurrent temozolomide (TMZ; 75 mg/m^2 daily) followed by six cycles of adjuvant TMZ (200 mg/m^2

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0936-6555/

for 5 days every 4 weeks). An overall median survival benefit of 2.5 months was observed in the chemotherapy arm and 5 year survival improved from 1.9% to 9.8%. This trial recruited patients aged 18e70 years, but the survival benefit in patients aged over 60 years failed to reach statistical significance [4].

The treatment of patients aged 70 years or over is not well defined. There is good evidence that radiotherapy improves survival without compromising quality of life when compared with best supportive care. However, the optimal dose and duration of radiotherapy is yet to be established [5e7]. Recent trials have shown equivalent survival outcomes for patients receiving radiotherapy alone compared with TMZ alone. Recently published data have suggested a significant survival benefit from adding concomitant and adjuvant TMZ to hypofractionated radiotherapy [8]. These studies also confirmed the predictive role of MGMT promoter methylation in determining which patients would probably benefit from TMZ alone [9,10]. The MGMT gene plays a role in repairing DNA damage inflicted by alkylating chemotherapy agents such as TMZ. Methylation of the promoter region represses gene transcription and increases TMZ sensitivity [11]. IDH1/2 mutation status has also emerged as a powerful prognostic biomarker. Mutations in the IDH1 or -2 genes are associated with secondary GBM and with significantly improved prognosis, independent of treatment received [12]. However, IDH mutation frequency is inversely correlated with patient age, so this biomarker is less useful in the older population [13].

Given the poor prognosis of older GBM patients, there is concern over the balance between survival benefits of treatment, which are often small, and treatment side-effects and quality of life. Deciding which patients would probably benefit from treatment is difficult and no validated tools are currently available. As well as disease-specific morbidity, pre-morbid factors play an important part in determining frailty and treatment tolerance. Recursive partitioning analysis has been studied in the older population and four prognostic subgroups were identified based on Karnofsky performance status and extent of surgical resection [14]. However, there were limitations to the availability of clinical and treatment factors included within this analysis. In the study presented here we investigated whether pre-morbid characteristics, disease-specific symptoms or tumour imaging features in a cohort of unselected older patients with GBM could predict for overall survival, after accounting for treatment variables.

Materials and Methods

Data Sources

After gaining ethical approval from the Health Research Authority, data were collected from three National Health Service (NHS) Trusts within the UK. All patients aged 70 years and over diagnosed with GBM at Brighton and Sussex University Hospitals NHS Trust, The Royal Marsden NHS Foundation Trust and The Beatson West of Scotland Cancer Centre in Glasgow between January 2010 and January 2015 were identified using local neuro-oncology patient databases, outpatient clinic lists and clinic letters.

Patients and Treatment

All patients were aged 70 years or over at the time of diagnosis. Diagnosis was made either by histopathological confirmation by a consultant neuropathologist if the patient underwent surgery or by consensus opinion in the multidisciplinary meeting setting based on clinical features and imaging as reviewed by a consultant neuroradiologist.

Clinical Characteristics

Follow-up schedules varied depending on the oncology centre, the treatment involved and the general condition of the patient, reflecting the lack of standardised clinical guidelines for this patient group. The date of diagnosis was taken as the date of the first brain scan showing radiological features of GBM.

Where available, the following data were recorded for all patients: comorbidities, current medications, Eastern Cooperative Oncology Group (ECOG) performance status [15] at diagnosis, marital status, presenting symptoms, neurological deficit, tumour location and imaging characteristics, degree of surgical resection, radiotherapy treatment dates and doses, and chemotherapy treatment dates and doses. The date of last follow-up and, where applicable, date of death were noted.

Comorbidities were classified according to the Charlson Comorbidity Index (CCI) [16]. A cut-off value of 3 was used to stratify patients. The number of medications taken by the patient was recorded; the G8 screening tool uses three as a significant number of medications but this was modified to five to take into account the likelihood of the patient being prescribed both dexamethasone and a proton pump inhibitor at diagnosis. Imaging characteristics of the tumours were documented from the consultant neuroradiologist's report of the initial diagnostic magnetic resonance imaging (MRI) or computed tomography scan. These reports were cross-referenced with multidisciplinary meeting (MDM) outcomes to check that no subsequent amendments had been made.

Surgical resection data were taken from the operation notes, immediate postoperative MRI scan and MDM discussion. Surgery was categorised as biopsy, subtotal tumour resection (STR) or total tumour macroscopic resection (TTR).

IDH1/2 mutation and MGMT promoter methylation status were not available for all patients who underwent surgery. During the study period it was not routine practice for these tests to be carried out. Different centres also use different assays to test for MGMT methylation status. Histopathological and molecular analysis is therefore being carried out in a centralised pathology laboratory on archival tumour surgical specimens retrieved from the patient cohort and will be presented separately.

Statistical Analysis

Descriptive statistics were used for cohort characteristics and treatment schedules. Overall survival was calculated from the date of diagnosis to the date of death from any cause, or last follow-up. Patients lost to follow-up or still alive were censored. The median survival of the cohort, with 95% confidence intervals, was determined using the Kaplan-Meier method.

Differences between groups were analysed by chi-square testing. In order to investigate relationships between pre-morbid and tumour characteristics and survival outcome, univariable analysis of overall survival was carried out using the Cox proportional hazards method to produce unadjusted hazard ratios with 95% confidence intervals. The assumptions for proportional hazard testing were met. Kaplan-Meier survival curves were produced for those covariates with significant hazard ratios. All factors were then included in a multivariate Cox proportional hazard regression model and backward stepwise selection used to refine this model. The degree of surgery was included within this model in order to account for those patients who had undergone radiological rather than histopathological diagnosis. Statistical significance was defined as a two-sided P value of 0.05. All analyses and calculations were carried out using SPSS v22.

Results

Patient Characteristics

In total, 339 patients met the eligibility criteria across the three sites; 192 (57%) were men and the median age at diagnosis was 75 (range 70-90) years. At the time of diagnosis, 225 (69%) patients had performance status 0-2. Three hundred and fourteen (97%) patients had a CCI less than or equal to 3 and 150 (46%) were taking five or fewer medications. Baseline characteristics are outlined in Table 1.

Two hundred and forty-one (71%) patients had an MRI scan at diagnosis, there being regional variation in scanning patterns. Two hundred and thirty (68%) patients met a neuro-oncologist in an outpatient setting compared with 109 (32%) who were discussed at an MDM and subsequently received best supportive care under the care of neurosurgical or inpatient medical, general oncology or palliative care teams.

One hundred and sixty-three (48%) patients had a radiological diagnosis of GBM and did not undergo surgery. Of these, 22 (13%) went on to receive palliative radiotherapy, the remainder receiving best supportive care. One hundred and seventy-six (52%) patients underwent a surgical procedure (Table 2). Of these, 68 (39%) had a biopsy, 71 (40%) underwent STR and 37 (21%) TTR. Of those who had surgery, 61 (34%) patients subsequently received best supportive care.

One hundred and twenty-two (36%) patients received radiotherapy. Of these, 18 patients were treated with 60 Gy in 30 fractions with concurrent TMZ (75 mg/m^2 daily) followed by adjuvant TMZ (200 mg/m^2 for 5 days every 4 weeks). Fifteen (83%) patients completed the concomitant regimen; three (17%) patients completed radiotherapy but discontinued TMZ before the end of radiotherapy because of fatigue. Of the 15 who completed concomitant TMZ, 12 continued to adjuvant TMZ. All of these patients received at least two cycles of adjuvant TMZ and four (25%) completed all six cycles. In the remaining patients, adjuvant TMZ was discontinued because of tumour progression, bone marrow toxicity or fatigue.

Six patients were treated with 'radical intent' radiotherapy alone, which was defined as doses of 54 Gy or greater; 97 patients received palliative radiotherapy, with 94 completing 30 Gy in six fractions and three patients 40 Gy in 15 fractions. One patient was treated with a twice daily regimen of 45 Gy in 20 fractions, but this was stopped after 14 fractions because of fatigue.

Table 1
Baseline patient characteristics

Age (years)		Comedications	
70-74	146 (43%)	<5	150 (46%)
75-79	111 (33%)	≥ 5	173 (54%)
80-84	56 (17%)		
85-89	25 (7%)	Presenting symptoms	
90-94	1 (<1%)	Confusion	127 (38%)
		Partial or full hemiparesis	118 (35%)
Gender		Visual disturbance	29 (9%)
Male	192 (57%)	Seizures	94 (29%)
Female	147 (43%)	Speech disturbance	114 (34%)
ECOG PS		Radiology	
0	23 (7%)	Left side	128 (38%)
1	105 (32%)	Right side	171 (50%)
2	97 (30%)	Bilateral	40 (12%)
3	75 (23%)	Midline shift	139 (42%)
4	27 (8%)	Mass effect	199 (60%)
		Single focus	246 (73%)
Marital status		Multifocal	84 (25%)
Single	92 (27%)	Gliomatosis	9 (3%)
Partner	186 (55%)	Hemispheric	310 (91%)
Unknown	61 (18%)		
		Seen by oncology	
Charlson Comorbidity Index		Yes	230 (68%)
3	314 (97%)	No	109 (32%)
> 3	9 (3%)		

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2
Treatment received

Treatment	Patients (% of whole cohort)
No surgery	163 (48%)
Biopsy	68 (20%)
Subtotal resection	71 (21%)
Total macroscopic resection	37 (11%)
First oncological treatment	
Best supportive care	202 (60%)
Palliative radiotherapy	91 (27%)
Radical radiotherapy	6 (2%)
Temozolomide alone	21 (6%)
Concurrent chemoradiotherapy	18 (5%)
Lomustine alone	1 (<1%)

Fifty-one (15%) patients received chemotherapy: 18 were treated with concurrent radiotherapy and TMZ, 16 with single-agent TMZ as first-line treatment and one with single-agent lomustine (CCNU) as first-line treatment; 16 patients received TMZ or PCV (procarbazine, lomustine and vincristine) as second-line, or salvage, treatment.

Survival

At follow-up in January 2016, 323 patients (95%) had died, with a median overall survival for the whole group of 3.8 months (range 0.1-62 months; 95% confidence interval 3.3-4.3 months). The probabilities of survival at 3, 6, 12 and 24 months were 62%, 34%, 13% and 4%, respectively.

Univariable Analysis

To investigate a relationship between individual factors and overall survival, a univariate analysis was carried out using Cox regression analysis (Table 3). Age was assessed using 5 year age brackets. Compared with those aged 70-74 years, patients aged 75-79 years (hazard ratio 1.36, P ¼ 0.017), 80-84 years (hazard ratio 2.01, P < 0.001) and 85-89 years (hazard ratio 2.32, P < 0.001) had a statistically

Table 3
Univariable analysis using Cox proportional hazards regression

Variable	P value	Hazard ratio	95% confidence interval for hazard ratio
Age range	<0.001		
75-79 versus 70-74	0.017	1.365	1.057-1.763
80-84 versus 70-74	<0.001	2.009	1.459-2.766
85-89 versus 70-74	<0.001	2.320	1.499-3.591
90-94 versus 70-74	0.063	6.550	0.903-47.502
ECOG categories	<0.001		
1 versus 0	0.138	1.430	0.891-2.296
2 versus 0	<0.001	2.431	1.505-3.926
3 versus 0	<0.001	3.237	1.977-5.301
4 versus 0	<0.001	3.163	1.779-5.624
Gender (male versus female)	0.824	0.975	0.782-1.216
Marital status (partner versus single)	0.336	0.882	0.683-1.139
CCI (3 versus >3)	0.276	1.481	0.731-3.001
Comedications (<5 versus ◆5)	0.572	1.067	0.852-1.336
Seizures	<0.001	0.618	0.481-0.795
Confusion	0.003	1.416	1.128-1.778
Hemiparesis	0.127	1.197	0.950-1.507
Visual disturbance	0.822	0.957	0.653-1.403
Speech disturbance	0.140	1.193	0.944-1.507
Side	0.008		
Right versus left	0.023	0.760	0.600-0.963
Bilateral versus left	0.249	1.241	0.860-1.793
Focality	0.822		
Multifocal versus single	0.551	1.240	0.612-2.510
Gliomastosis versus single	0.623	1.200	0.579-2.488
Hemispheric	0.016	0.616	0.414-0.915
Mass effect	0.035	1.277	1.018-1.603
Midline shift	0.290	1.129	0.902-1.414
First treatment received	<0.001		
Palliative RT versus BSC	<0.001	0.434	0.336-0.561
Radical RT versus BSC	0.011	0.316	0.129-0.769
TMZ alone versus BSC	<0.001	0.246	0.149-0.408
CRT versus BSC	<0.001	0.152	0.086-0.270
CCNU versus BSC	0.793	0.769	0.108-5.495
Radiotherapy regimens	<0.001		
30/6 versus 0	<0.001	0.478	0.372-0.613
40/15 versus 0	0.087	0.295	0.073-1.193
54/30 versus 0	0.484	0.608	0.151-2.452
60/30 versus 0	<0.001	0.198	0.118-0.332
other versus 0	0.495	1.984	0.277-14.230
Surgery	<0.001		
Biopsy versus nothing	<0.001	0.572	0.428-0.765
STR versus nothing	<0.001	0.436	0.325-0.585
TTR versus nothing	<0.001	0.320	0.218-0.470

ECOG, Eastern Cooperative Oncology Group; CCI, Charlson Comorbidity Index; RT, radiotherapy; BSC, best supportive care; TMZ, temozolomide; CRT, chemoradiotherapy; CCNU, lomustine; STR, subtotal tumour resection; TTR, total tumour macroscopic resection.

significant increased risk of death (comparing each group with any other at any time point).

An ECOG performance status of 2 (hazard ratio 2.43, P < 0.001), 3 (hazard ratio 3.24, P < 0.001) or 4 (hazard ratio 3.16, P < 0.001) compared with 0 (Figure 1), presenting with confusion (hazard ratio 1.48, P ¼ 0.003) and the presence of mass effect on the diagnostic scan (hazard ratio 1.28, P ¼ 0.035) were significantly associated with an increased risk of death. Presenting with seizures (hazard ratio 0.62, P < 0.001), right-sided tumours (hazard ratio 0.76, P ¼ 0.023) and tumours confined to the cerebral hemisphere (hazard ratio 0.62, P ¼ 0.016) were significantly associated with a decreased risk of death.

Considering treatment effects, patients who underwent any surgery had a statistically significant decreased risk of death (hazard ratio 0.49, P < 0.001) that was proportional to the degree of resection carried out (biopsy hazard ratio 0.57, P < 0.001; STR hazard ratio 044, P < 0.001; TTR hazard ratio 0.32, P < 0.001). The median overall survival in those without surgery was 2.6 months (interquartile range 1.4-5.0 months) compared with 3.9 months (interquartile range 2.4-9.1 months) for biopsy, 7.2 months (interquartile range 3.8-10.0 months) for STR and 8.2 months (interquartile range 3.8-16.7 months) for TTR.

Those who received active oncological treatment (radiotherapy and/or chemotherapy) had a decreased risk of death. The median overall survival for those offered only best supportive care was 2.5 months (interquartile range 1.4-4.5 months) compared with 6.8 months (interquartile range 3.6-10.7 months) for palliative radiotherapy, 13.1 months (interquartile range 3.8-15.4 months) for single-agent TMZ, 9.7 months (interquartile range 6.7-10.7 months) for radical radiotherapy and 16.7 months (interquartile range 8.8-33.7 months) for radical chemo-radiotherapy (Figure 2).

Multivariate Analysis

In the multivariate analysis, pre-treatment characteristics predicting for overall survival that remained significant included ECOG performance status, presenting with seizures, tumours confined to the cerebral hemisphere, radiological evidence of mass effect, multifocal tumours or gliomatosis, with the last three being associated with poorer survival (Table 4).

As ECOG performance status increased from 0 to 4, the hazard ratio for death also increased in a stepwise manner. ECOG performance status 1 inferred a 66% increased risk of death compared with ECOG performance status 0 (P ¼ 0.042), ECOG performance status 2 78% (P ¼ 0.031), ECOG performance status 3120% (P ¼ 0.008) and ECOG performance status 4140% (P ¼ 0.021). The presence of mass effect on the diagnostic MRI or computed tomography scan also predicted for a 31% increased risk of death (P ¼ 0.049).

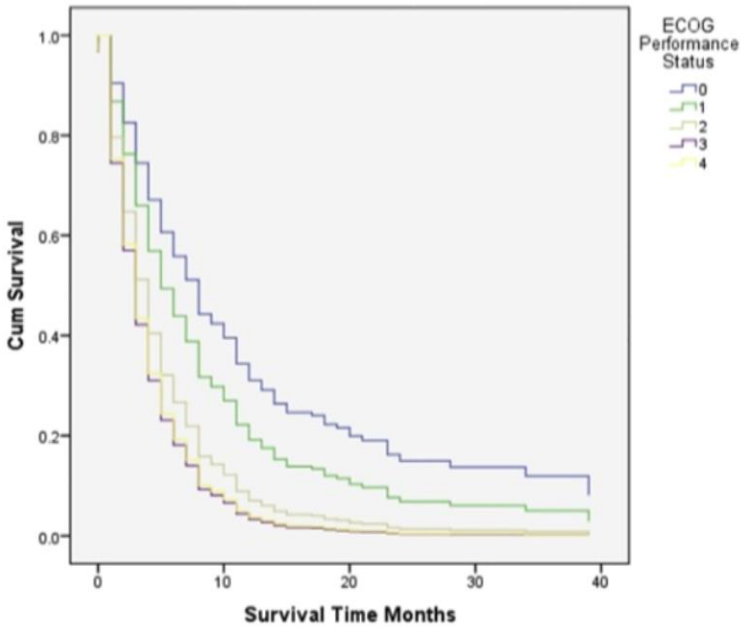

Fig 1. Overall survival in months, stratified by Eastern Cooperative Oncology Group (ECOG) performance status.

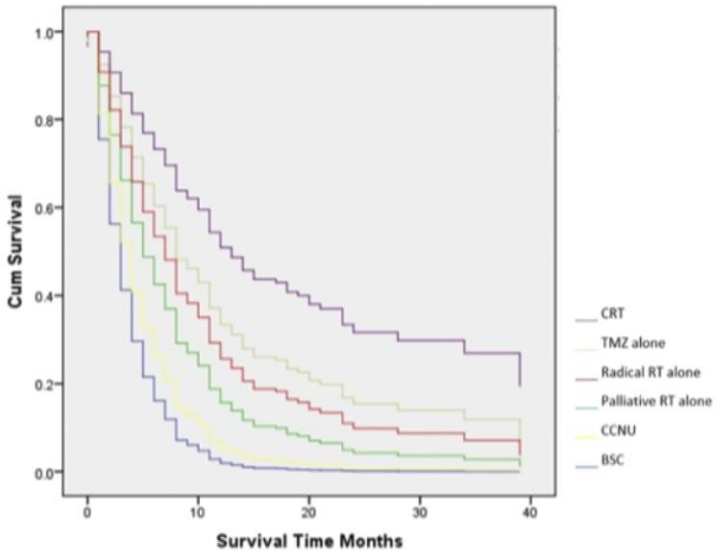

Fig 2. Overall survival in months, stratified by first treatment received.

Table 4
Multivariable Cox proportional hazards model of factors predictive of overall survival

Variable	P value	Hazard ratio	95% confidence interval for hazard ratio
ECOG categories	0.104		
1 versus 0	0.042	1.664	1.020-2.716
2 versus 0	0.031	1.780	1.053-3.008
3 versus 0	0.008	2.198	1.227-3.936
4 versus 0	0.021	2.409	1.141-5.086
Seizures	0.001	0.632	0.478-0.834
Focality	0.002		
Multifocal versus single	0.013	3.419	1.296-9.023
Gliomastosis versus single	0.124	2.082	0.817-5.303
Hemispheric tumour	0.048	0.594	0.355-0.996
Mass effect	0.049	1.307	1.002-1.705
First treatment	<0.001		
Palliative RT versus BSC	0.005	0.588	0.407-0.850
Radical RT versus BSC	0.119	0.468	0.180-1.217
TMZ alone versus BSC	0.004	0.395	0.211-0.739
CRT versus BSC	<0.001	0.189	0.089-0.402
CCNU versus BSC	0.395	2.458	0.310-19.472
Surgery	0.049		
Biopsy versus nothing	0.373	0.849	0.593-1.217
STR versus nothing	0.019	0.625	0.421-0.927
TTR versus nothing	0.019	0.560	0.345-0.909

ECOG, Eastern Cooperative Oncology Group; RT, radiotherapy; BSC, best supportive care; TMZ, temozolomide; CRT, chemoradiotherapy; CCNU, lomustine; STR, subtotal tumour resection; TTR, total tumour macroscopic resection.

Presenting with seizures conferred a protective influence with a decreased risk of death of 37% (P ¼ 0.001). Similarly, presenting with a hemispherically located tumour decreased the risk of death by 41% (P ¼ 0.048). These effects were independent of surgical variables.

Presenting with multifocal disease or gliomatosis compared with a single focus of visible disease on the diagnostic computed tomography or MRI scan was significantly associated with an increased risk of death in multivariate analysis. Those patients with multifocal disease or

gliomatosis were less likely to receive any form of debulking surgery (chi-squared P ¼ 0.015).

The extent of surgery was significantly associated with a decreased risk of death. Undergoing a STR decreased the risk of death by 37% (P ¼ 0.019) and a TTR decreased risk by 44% (P ¼ 0.019) compared with no surgery.

After accounting for surgery, the risk of death increased significantly with best supportive care compared with active treatment options. Palliative radiotherapy decreased the risk of death by 41% (P ¼ 0.005), TMZ alone by 60% (P ¼ 0.004) and radical chemoradiotherapy by 81% (P < 0.001). The use of radical radiotherapy alone or lomustine chemotherapy alone was not statistically significant (there were very low numbers of patients in these groups).

Discussion

The treatment of older patients with GBM remains a contentious topic. Since the EORTC trial of 2005, the academic community has recognised a dearth of evidence among this vulnerable cohort. The number of prospective trials within this group remains low, although radiotherapy schedules have been examined, notably in the trials by Keime-Guibert et al. [6] and subsequently by the International Atomic Energy Agency [5,7]. The role of single-agent TMZ has been explored with the publications of the NOA-08 [9] and NORDIC [10] studies. The EORTC study of the addition of concomitant and adjuvant TMZ to hypofractionated radiotherapy has shown a progression-free and overall survival benefit for the combination, highly statistically significant in those with MGMT methylation and particularly pronounced in those over the age of 70 years. Quality of life was similar in the two groups and haematological toxicity in the chemotherapy group was manageable. The patients treated in the trial, however, seem to be fitter than the 'average' older patient presenting with GBM, as 76.9% were of performance status 0 or 1, 68.3% underwent a partial or complete surgical resection, the median Mini-Mental State Examination score was 27/30, a quarter of the patients had no requirement for steroids and 40% were well enough to receive second-line therapy [8]. When assessing an older patient recently diagnosed with GBM, it remains difficult to decide whether he or she is fit enough to withstand the toxicities associated with the various treatment options and therefore gain the associated modest survival benefit, without significant detriment to quality of life.

There has been recent international focus on older patients with cancer [17], with studies across different tumour groups looking at embedding detailed assessments of older patients within the outpatient setting. The 'geriatric assessment', a holistic approach to examining the older patient, incorporates domains such as social situation, mobility, comorbidities, cognition, fatigue and nutrition. It has been shown to predict for tolerance to treatment and overall survival in mixed populations of lung, colorectal, gynaecological and breast cancer patients [18-21]. No such work has yet been carried out within the neuro-oncology arena. This study aimed to explore whether retrospectively analysed pre-treatment clinical and radiological characteristics could predict for survival. There was no effect of comorbidities or comedications on outcome, although performance status remained significant on multivariable analysis. As seen in a similar Canadian study [21], presenting with seizures conferred a survival advantage that is probably explained by earlier presentation and an absence of neurological deficits.

Radiological assessment by an experienced neuroradiologist can provide prognostic information. Patients with tumours located outside of the cerebral hemispheres, evidence of mass effect and multifocal disease or gliomatosis on the diagnostic scan were found to have poorer outcomes. The presence of more than a single focus of disease correlated with a decreased likelihood of surgical debulking, although the other factors were independent prognostic indicators.

The main prognostic factors previously used to stratify GBM patients have been age and performance status [22]. This study showed that increasing age was not significant when performance status and treatment factors were accounted for. In line with other studies, patients treated with surgical debulking had improved outcomes compared with those with biopsy or no surgery [23,24]. Similarly, those patients treated with radical chemoradiotherapy (albeit small numbers) had the greatest survival benefit of all treatment modalities. This supports the argument that chronological age alone should not be used to determine treatment offered, as it is a poor representative of physiological reserve [25,26].

Although this was a retrospective series, with the inherent biases associated with such analyses, its large size and multicentre approach has produced findings that may provide some guidance for evaluating which patients will benefit from more aggressive treatment. In order to represent a realistic assessment of UK practice, all patients with a diagnosis of GBM, either by histological or radiological verification, were included and our model adjusted for this variable. There is selection bias in place whereby only 'healthier' patients were selected for surgery and we see this in the small numbers of radiologically diagnosed patients who proceeded to any active treatment. However, the inclusion of all patients enabled overall survival figures to be calculated that are representative of the true state of older GBM patients within the UK rather than only those who are well enough for an operation and histopathological diagnosis. Our survival data are consistent with those obtained by national database interrogation [3]. This is, to the authors' knowledge, the largest UK-basedretrospective review incorporating details of clinical presentation, comorbidities and imaging characteristics within the older cohort of GBM patients. This retrospective data plus prospectively collected data will be used to develop a prognostic/predictive tool to guide treatment.

This study was subject to the limitations common to all retrospective reviews; in particular, treatment-related toxicities were not assessed because of a lack of consistent

information. We were also unable to assess quality of life for our patients, arguably equally as valid an end point as overall survival among this population. Another limitation is the lack of data on pathological biomarkers, including IDH1/2 mutation and MGMT promoter methylation status. Although there are some controversies over the best assay for MGMT promoter methylation, the prognostic value of this biomarker has been consistently shown in GBM patients of all ages [27,28]. MGMT data were only available for 58% of our study patients as it was not being carried out routinely in all centres throughout the study period. A more detailed analysis of the molecular landscape of the tumours in this study is currently underway.

Conclusion

Older patients with GBM remain an under-researched population and continue to have a poorer prognosis than their younger counterparts. Treatment options are available within this cohort but clinical assessment and treatment decision making remain non-standardised. This study shows that performance status, clinical presentation and imaging characteristics are prognostic for survival outcomes, irrespective of age or treatment received. Further work is needed to provide detailed prospective assessments of older GBM patients, enabling the development of clinical, radiological and biological prognostic and predictive biomarkers.

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Figure 26: Chapter 3 as published in the Journal of Geriatric Oncology

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Short communication

Glioblastoma in the elderly — How do we choose who to treat?

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ABSTRACT

Objective: Glioblastoma (GBM) is the commonest primary malignant brain tumour amongst the adult population. Incidence peaks in the 7th and 8th decades of life and as our global population ages, rates are increasing. GBM is an almost universally fatal disease with life expectancy in the range of 3–5 months amongst the elderly.

Materials and Methods: The assessment of elderly GBM patients prior to treatment decisions is poorly researched and unstandardised. In order to begin tackling this issue we performed a cross-sectional survey across all UK based consultant neuro-oncologists to review their current practice in assessing elderly GBM patients.

Results: There were 56 respondents from a total of 93 recipients (60% response rate). All respondents confirmed that at least some patients aged 70 or over were referred to their clinics from the local multidisciplinary team meeting (MDT). Only 18% of consultants routinely performed a cognitive or frailty screening test at initial consultation. Of those who performed a screening test, the majority reported that the results of the test changed their treatment decision in approximately 50% of cases. Participants ranked performance status as the most important factor in determining treatment decisions.

Conclusions: Considering the heterogeneity of this patient population, we argue that performance status is a crude measure of vulnerability within this cohort. Elderly GBM patients represent a unique clinical scenario because of the complexity of distinguishing neuro-oncology related symptoms from general frailty. There is a need for specific geriatric assessment models tailored to the elderly neuro-oncology population in order to facilitate treatment decisions.

1. Introduction

Glioblastoma (GBM) is the commonest primary malignant brain tumour amongst the adult population with approximately 2000 new cases diagnosed in the UK per year. Incidence peaks in the 7th and 8th decades of life and as our global population ages, rates are increasing. Outcomes from this disease remain poor with median life expectancy in England at 6.1 months, dropping to 3.2 months amongst those aged over 70.[1]

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Given the poor prognosis in this group, treatment must be balanced against side effects and worsening quality of life. Treatment in those under 70 was standardised by the landmark EORTC 26981 trial, showing a 2 month survival benefit and a doubling of 2 year survival rates with concurrent radiotherapy (RT) and temozolomide (TMZ) chemotherapy followed by 6 months of adjuvant TMZ. The age cut off for this trial was 70, however in the group of trial patients over the age of 65 the benefit of adding chemotherapy to radiotherapy was not statistically significant.[3] There is concern that long course chemotherapy and radiotherapy may in fact be detrimental to elderly and frail patients.

In patients aged 70 or over there is a lack of consensus on standard of care. Radiotherapy has a survival advantage over best supportive care[3] however the optimal dose of radiotherapy is yet to be established with a recent International Atomic Energy Agency study suggesting non-inferiority of shorter regimes in the palliative setting.[4] A recent Phase III trial randomised elderly GBM patients to standard radiotherapy with 60 Gy in 30#, hypofractionated radiotherapy of 34 Gy in 10# or TMZ chemotherapy alone. For patients older than 70, survival was significantly longer with TMZ or hypofractionated radiotherapy than with standard radiotherapy.[5] Those with defects in the DNA repair protein MGMT did significantly better in the chemotherapy arm than those with intact MGMT, a result which was replicated in the NOA-08 trial which randomised elderly GBM patients to standard radiotherapy with 60 Gy in 30# or TMZ alone. This non-inferiority trial showed TMZ to be a suitable monotherapy option, with greater effect seen in those with MGMT promoter methylation.[6] There is now evidence to support the use of chemotherapy or radiotherapy as single agents amongst elderly GBM patients and an increasing interest in using MGMT promoter methylation status as a biomarker. However there remains a paucity of data surrounding the clinical basis by which individual patients are assessed for treatment.

Assessment of older patients with GBM is challenging due to the mix of tumour-related symptoms and pre-existing comorbidities, and it can be difficult to predict which patients will benefit from active treatment. Multi-dimensional geriatric assessment has been shown to predict for tolerance to treatment and survival in other tumour types.[7] It is apparent that the assessment tools used in oncology patients with extra-cranial malignancies are likely to be less valid within the GBM cohort because of the unique and potentially isolated deficits caused by the disease itself. As yet there is a paucity of trial data assessing the benefit of geriatric assessment in determining treatment options and providing a prognostic scoring system amongst elderly neuro-oncology patients. In order to begin addressing this issue we performed a cross-sectional survey of all UK based consultant neuro-oncologists, to review their current practice in assessing elderly GBM patients.

2. Materials and Methods

2.1. Study Design

A short cross-sectional survey design was used. Data were collected from November to December 2015.

2.2. Participants

The survey aimed to capture the views of all currently practising consultant neuro-oncologists in the UK. Consultant neuro-oncologists were defined by practice patterns and attendance at local MDTs and were identified from conference attendances, The Brain Tumour Charity database and direct telephone contact with secretaries working at all of the oncology centres within the UK. E-mail addresses were collated and a link to the online survey sent to each. 93 participants were identified in total. Participants were excluded if not currently practising due to long term illness, maternity leave or having retired.

2.3. Questionnaire

The questionnaire was designed by the principal investigator and the validity of the questions assessed by 3 consultant co-investigators from 3 different centres. The survey was kept purposefully short in order to increase the likelihood of a high response rate. The first section aimed to assess the local referral systems for elderly GBM patients to oncology clinics. The second and third sections concentrated on how clinicians currently assess elderly GBM patients and how importantly they rank certain clinical, pathological and radiological characteristics (see Table 2). The final section assessed local access to multidisciplinary team support including physiotherapists, occupational therapists and speech and language teams within the outpatient setting.

2.4. Data Collection and Analysis

A link to the online survey was e-mailed to all participating consultant neuro-oncologists. 2 subsequent reminder e-mails were sent. As the survey was anonymised to prevent reporting bias, it was not possible to identify the non-responders to remind them further. Data was analysed using Microsoft Excel 2010.

2.5. Ethical Considerations

The survey was supported by The Brain Tumour Charity and the NCRI Brain Tumour Clinical Studies Group. No financial aid was given. The survey was voluntary, anonymous, aimed only at healthcare professionals and therefore was not considered to require IRB approval.

3. Results

3.1. Responses

There were 56 responders resulting in an overall response rate of 60%.

3.2. Referral to Oncology Services

Respondents assessed on a 5 point Likert scale how many patients aged 70 or over discussed at their local multidisciplinary meeting were subsequently referred to their oncology outpatient services. All participants replied that at least some

Table 1 – What proportion of the patients over the age of 70 who are discussed at your local MDT with a new diagnosis of likely GBM are seen in your neuro-oncology clinic?

	Respondents
None of them	0
Some of them	8 (14%)
About half of them	10 (18%)
Most of them	26 (46%)
All of them	11 (20%)
Skipped question	1 (2%)

of those discussed were referred. 20% of participants saw all patients aged 70 or over (Table 1).

3.3. Assessment of Domains

85% of respondents valued performance status as 'extremely important' when assessing elderly GBM patients for treatment, a higher proportion than for any other factor. This was followed by co-morbidities then age over 80. One respondent commented 'treatment has to be very individualised in glioma patients and cognitive impairment, frailty and informed patient choice are the most important factors.' Despite the publication of the NORDIC and NOA-08 trials, there was a marked difference in how responders ranked the importance of MGMT methylation status. 6% of responders do not routinely test for MGMT status whereas 48% feel that MGMT status is very or extremely important. The availability of clinical trials was felt to be least important (Table 2).

3.4. Cognitive and Frailty Screening

80% of respondents do not routinely perform a formal cognitive or frailty screening test on elderly GBM patients in clinic. 2% were unsure and of the 18% that do perform a test, the most common is the Mini-Mental State Examination. Other tests mentioned include the Montreal Cognitive Assessment and the Abbreviated Mental Test Score. 57% of those who do use a test feel it changes the decision made at local MDT around half the time.

3.5. Availability of Multidisciplinary Support

31% of respondents had access to one or more of physiotherapy, occupational therapy or speech and language services during outpatient clinics. 70% of those who had services available felt that their assessment rarely changed the initial treatment decision. A number of respondents commented on the importance of the clinical nurse specialist in aiding in treatment decisions and enhancing communication between members of the MDT.

4. Discussion

This is the first study looking at how patients aged 70 and over with GBM are currently assessed across UK neuro-oncology clinics. There is a growing need to improve outcomes amongst elderly oncology patients. Chronological age alone is insufficient to predict for fitness, frailty or tolerance to treatment and under treatment is one of a number of reasons why elderly oncology patients do less well.[8] We have shown that in one third of the UK neuro-oncology MDTs represented in this survey, only 50% of the elderly GBM patients discussed ever meet a neuro-oncologist.

While previous work has suggested that performance status is a blunt tool for detecting the subtle and nuanced symptoms that GBM can evoke,[9] it was defined as 'extremely important' in determining treatment decisions by a large majority of participants in our survey. Although this is consistent with international data, the International Society of Geriatric Oncology recommended in 2015 that a geriatric screening assessment be performed on elderly oncology patients to assess for referral for a full geriatric assessment.[10] As displayed by this survey, in neuro-oncology clinics this is yet to occur with 80% of respondents not routinely performing a cognitive or frailty test. The reasons for this are likely multifactorial including a lack of time and awareness but a key aspect may be the lack of a standardised and well validated tool for this cohort. The need for geriatric assessment screening tools within neuro-oncology is validated by the participants, 50% of whom who felt a screening assessment changed their decision making half of the time.

Perhaps unsurprisingly, the survey displays the national heterogeneity in oncological services in terms of referrals from MDTs and availability of physiotherapy, occupational therapy and speech and language services. More interesting was the view, from those who did have access, that these assessments very rarely changed the initial management

Table 2 – When assessing a new patient aged 70 or over with a glioblastoma, how would you rate the following parameters in determining the treatment you offer?

	Not important	Slightly important	Moderately important	Very important	Extremely available	Not important
Age 70–75	8%	23%	40%	17%	12%	0%
Age 75–80	0%	10%	33%	38%	19%	0%
Age > 80	0%	0%	15%	50%	35%	0%
Performance status	0%	0%	0%	15%	85%	0%
Co-morbidities	0%	4%	15%	37%	44%	0%
Family support network	0%	27%	40%	25%	8%	0%
Extent of surgical resection	2%	17%	54%	19%	8%	0%
MGMT status (if applicable)	4%	15%	27%	29%	19%	6%
Availability of clinical trials	17%	19%	23%	21%	14%	6%
Size of tumour and imaging features	0%	12%	30%	42%	16%	0%

decision. It was beyond the scope of this survey to assess the potential benefit from early involvement of a multidisciplinary team. Limitations of this study include response bias as those who are interested in geriatric oncology may have been more likely to participate. As it was anonymous it was not possible to explore further any individual or geographical distribution to the response rate. We aimed to include all UK based consultant neuro-oncologists however this is a relatively small sample in the international population and results may not be transferrable to different nations.

Despite a handful of recent trials focusing on elderly GBM patients, management of this cohort continues to prove challenging. Previous reports have identified multiple pre-treatment prognostic factors including molecular characteristics (notably MGMT and IDH status), comorbidities, neurological status, location of lesion, marital status, language deficit and radiological features. Few of these trials were designed specifically for the older cohort of patients.

Treatment options until recently for elderly GBM patients included palliative short course radiotherapy or best supportive care. The results from the NOA-08 and NORDIC trials suggest an effective alternative of single agent TMZ amongst those whose tumours show methylation of MGMT, reserving radiotherapy (and its attendant toxicity) for subsequent progression. Treatment initiation decisions however are still highly subjective. There remains an urgent need to develop and validate a customised neuro-oncology based assessment tool for this vulnerable patient group and to determine its prognostic and predictive value in a prospective study. Such a tool could incorporate components of the geriatric assessment alongside pathological and radiological markers. We are aiming to pilot such an assessment tool in a UK based feasibility study later this year. As respondents from our survey commented, 'assessing how intensive to be is very difficult' and 'using a frailty or cognitive test result as an essential part of the referral might improve selection of patients'.

Disclosures and Conflict of Interest Statements

F. Saran serves on the advisory panel on glioblastoma for Roche and has received honoraria from Roche. A. Chalmers has received honoraria from Boehringer Ingelheim and ChemoCentryx, has research support from Astra Zeneca, and has received remunerations from Sentinel Oncology. J. Brock has received remunerations from Boehringer Ingelheim.

Author Contributions

Concept and design: CF Lorimer, F Saran, AJ Chalmers, J Brock.
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Analysis and interpretation of data: CF Lorimer.
Manuscript writing and approval: CF Lorimer, F Saran, AJ Chalmers, J Brock.

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