**Title**

 Glioblastoma in the Elderly – how do we choose who to treat?

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**Abstract**

Glioblastoma (GBM) is the commonest primary malignant brain tumour among the adult population. Incidence peaks in the $7^{th}$ and $8^{th}$ 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.

The assessment of elderly GBM patients prior to treatment decisions is poorly researched and unstandardized. 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.

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.

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.

**Introduction**

Glioblastoma (GBM) is the commonest primary malignant brain tumour among the adult population with approximately 5,000 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].

Given the poor prognosis in this group, treatment must be balanced against side effects and worsening quality of life. Treatment in those under 65 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 and, in the group of trial patients over the age of 65, the benefit of adding chemotherapy to radiotherapy was not statistically significant[2]. 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. A recent Phase III trial randomised elderly GBM patients to standard radiotherapy with 60Gy in 30#, hypofractionated radiotherapy of 34Gy in 10# or TMZ chemotherapy alone. For patients older than 70, survival was significantly longer with TMZ or hypofractionated radiotherapy than with standard radiotherapy[4]. 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 60Gy 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[5]. 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[6]. 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.

**Materials and methods**

Study design

A short cross-sectional survey design was used. Data were collected from November to December 2015.

Participants

The survey aimed to capture the views of all currently practising consultant neuro-oncologists in England, Scotland, Wales and Northern Ireland. The participants 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.

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. The final section assessed local access to multidisciplinary team support within the outpatient setting.

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 it was not possible to identify the non-responders to remind them further. Data was analysed using Microsoft Excel 2010.

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.

**Results**

Responses

There were 56 responders resulting in an overall response rate of 60%. The survey was anonymised so it was not possible to assess the geographical spread of responders.

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 of those discussed were referred. 20% of participants saw all patients aged 70 or over (Table 1).

Assessment of domains

Respondents valued performance status as the most important parameter when assessing elderly GBM patients for treatment. This was followed by age over 80 and co-morbidities. One respondent commented *'treatment has to be very individualised in glioma patients and cognitive impairment, fraility 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).

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.

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 to *'make the connections'* with other members of the MDT.

**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 worse[7]. We have shown that in a third of UK neuro-oncology MDTs in this survey, only 50% of the elderly GBM patients discussed ever meet an oncologist.

While previous work has suggested that performance status is a blunt tool for detecting the subtle and nuanced symptoms that GBM can evoke[8], participants ranked performance status as the most important factor in determining treatment decisions. 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[9]. As displayed by this survey, in neuro oncology clinics this is yet to occur with 80% of respondents not performing a cognitive or frailty test routinely. The reasons for this are likely multifactorial including a lack of time and awareness[10] 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 decision. It was beyond the scope of this survey to assess the potential benefit from early involvement of a multidisciplinary team.

Despite a handful 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 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. 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'*

**Tables**

**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%) |

**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 important | Not available |
|---|---|---|---|---|---|---|
| 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% |

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