Glioblastoma

Glioblastoma: Clinical presentation, diagnosis and management

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Competing interests

We have read and understood the BMJ policy on declaration of interests and have no relevant interests to declare.

What you need to know

1. Early symptoms of brain tumours in adults are non-specific and patients may present multiple times to primary care services before they are referred for investigation. Look out for symptoms of raised intracranial pressure (e.g. headaches exacerbated by lying down, triggered by Valsalva maneuver or associated with vomiting or visual disturbance), combinations of symptoms (e.g. headache *plus* cognitive impairment, headache *plus* weakness, headache *plus* personality change) and symptoms which progress over time. New-onset focal or generalized seizures in adulthood also warrant investigation for a brain tumour.
2. In patients with symptoms or signs suggestive of a brain tumour, arrange an urgent MRI head with and without contrast through a rapid-access 'suspected cancer' pathway, when available. In patients with suspicion of raised intracranial pressure, arrange a same-day clinical assessment and contrast-enhanced CT head scan.
3. Glioblastoma (GBM) is the most common primary brain cancer. Standard treatment includes maximal safe resection followed by concomitant radiotherapy and temozolomide (TMZ) chemotherapy and then adjuvant TMZ. Disease progression is expected in all cases and consideration of further treatment should take into account the patient's performance status, tumour size, location and time since first treatment
4. Key supportive medications may include corticosteroids for vasogenic oedema and anti-epileptic medication if seizures occur
5. Due to the incurable and rapidly progressive nature of glioblastoma, close collaboration between multidisciplinary teams in tertiary care hospitals and primary care services is recommended. Early involvement of GPs and specialist community palliative care teams can assist patients and caregivers with advance care planning as well as management of symptoms, physical and cognitive impairment, communication difficulties and the innate uncertainties about disease progression.

Glioblastoma (GBM) is the most common primary brain cancer in adults (1). Despite surgical resection, chemotherapy and radiotherapy, median survival after diagnosis is only 14-16 months (1–3). Disease progression is inevitable and results in worsening physical and cognitive disability, with early dependence on support from carers, general practitioners and palliative care services. Non-specialists play an important role from early referral of patients with suspected brain tumours, psychological support following diagnosis, management of medications and supportive care towards the end of life, and into bereavement for relatives. In this clinical update, we review the clinical presentation, investigation and management of patients with GBM.

What is glioblastoma?

GBM is a primary brain cancer which can arise anywhere within the central nervous system (CNS) but is most commonly located in the frontal or temporal lobes (4). Its origin within the CNS distinguishes it from the more common secondary brain cancers which occur due to metastasis from distant primary sites, most commonly lung, breast or skin (5). GBM belongs to a heterogeneous collection of brain tumours termed gliomas, which are thought to derive from glial cells or their precursors, and include astrocytomas and oligodendrogliomas (6). The former are classified by the World Health Organisation (WHO) as localised (grade I) or diffuse (grades II-IV), with increasing grade reflecting more aggressive tumour phenotypes (7). GBM is a grade IV diffuse astrocytoma, a highly malignant subtype with high rates of cell division, vascular proliferation and central areas of tumour necrosis (7,8).

How common is it?

GBM has an annual incidence of 3-5 per 100, 000 people (3,9,10). While the disease can occur in children and adults, median age at diagnosis is 65 years (9). It is approximately 1.6 times more common in males than females, the reason for which remains uncertain (3,9).

What are the risk factors?

The vast majority of patients with GBM do not have any identifiable risk factors for tumour development (11). Some rare familial cancer syndromes including neurofibromatosis type 1, tuberous sclerosis, Lynch syndrome and Li-Fraumeni syndrome are associated with an increased risk of GBM (12). Suspicion of an inherited cancer syndrome should prompt referral to a clinical geneticist to guide further investigation and follow-up. The only established non-genetic risk is a history of exposure to ionising radiation (13). Atopic conditions have been

identified as a protective factor, reducing the risk of glioma by approximately 30% (13). Epidemiological evidence does not support an association between use of cellular telephones and risk of brain tumour development (13).

How do patients present in primary care?

The initial presentation of patients with GBM is frequently non-specific, with broadly similar signs and symptoms seen with other primary or secondary brain tumours, as well as more common benign neurological conditions. Approximately half of patients are diagnosed following an emergency hospital presentation (14). Most will have attended their GP with symptoms prior to diagnosis, often on multiple occasions (15,16). Despite this, only 2% of patients in England are currently diagnosed via the 'suspected cancer' pathway which provides GPs with direct access to magnetic resonance imaging (MRI) brain scans within two weeks (14,16). This reflects the significant challenge of identifying suspected cases of brain tumours in primary care, where early symptoms often overlap with common benign conditions. In the UK, introduction of a national awareness campaign to improve recognition of early symptoms of brain tumours in children (HeadSmart) has reduced the time interval from onset of symptoms to diagnosis (17). An equivalent strategy for adult patients is yet to be developed.

Headache is the most common early symptom of brain tumours [**Figure 1**], but as few as 1-2 in 1000 patients who consult their GP with this symptom are later diagnosed with a brain tumour (18–20). Headache characteristics vary based on tumour location, size and rate of growth (21,22) and can be 'tension-type' or migrainous in nature. They tend to be exacerbated by supine position and are therefore most noticeable on waking. Headaches can also be precipitated by coughing or Valsalva manoeuvre. They tend to increase in frequency or severity over time. The development of additional neurological symptoms or signs in combination with headaches significantly increase the likelihood of an underlying brain tumour [**Figure 1**]. For example, new headache reported alongside weakness or cognitive dysfunction increase the likelihood of a brain tumour by 44 and 59-fold, respectively (18).

Seizures are a presenting symptom in approximately 20% of patients with GBM and an additional 20% develop seizures later in the disease (11,23). While a less common presentation in the primary care setting, new onset seizure in adulthood has the greatest positive predictive value (PPV) of all individual symptoms (1.6%), followed by motor weakness (1.5%) and confusion (1.4%) (18). Various other presenting symptoms have been linked to brain tumours

[**Figure 1**], however each has a PPV of less than 1% (18). Combinations of symptoms, especially if progressive in nature, significantly increase the likelihood of an intracranial tumour being identified on MRI scan (24,25).

What to cover on initial assessment?

History: Establish the nature and temporal progression of the presenting symptoms. A collateral history from family members, friends or work colleagues can be very informative since patients are often unaware of subtle changes in personality or behaviour over time (26). A recent qualitative study of patient experiences of brain tumour diagnosis found that most patients and family members had noticed multiple mild symptoms or 'changes' (e.g. "My head felt fuzzy", "You weren't quite yourself") at least 6 months before their initial presentation (16). It is therefore important to review recent consultation records and empower patients who are not referred to keep a symptom diary and return if they feel something is still wrong (16,18).

For patients presenting with headache, inquire about high-risk clinical features which raise suspicion of a possible brain tumour [**Box 1**]. Also ask if there is any history of systemic malignancy, previous radiation exposure or family history of inheritable cancer syndromes which independently increase the likelihood of a brain tumour diagnosis (27,28). Focal neurological deficits associated with brain tumours usually develop gradually over the course of weeks to months; acute deficits are more likely related to cerebrovascular ischaemia or haemorrhage in the tumour. If a possible seizure is reported, inquire about preceding aura, a description of the event, as well as the presence of any tongue-biting, incontinence, post-ictal confusion or fatigue. Temporal lobe seizures are often missed since they present as an abrupt change in a patient's behaviour rather than tonic-clonic limb movements. They may be preceded by the sensation of an abnormal smell/taste or feeling of gastric uprising. When a history of seizure is suspected, patients should be given advice to avoid potentially dangerous work or leisure activities and told to stop driving while awaiting confirmation of diagnosis by a specialist. Family or caregivers, should be offered first aid advice on how to recognise and manage further seizures if they occur.

Examination: Perform a neurological examination of the cranial nerves, motor, sensory and cerebellar systems. In patients with symptoms suggestive of elevated intracranial pressure (ICP), examine the optic discs for signs of papilloedema or refer to local optician services for digital retinal photography. Routine use of cognitive screening tests such as the Mini Mental

State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) is not recommended since they lack sensitivity to detect subtle, domain-specific neurocognitive deficits in patients with GBM (29,30).

What differential diagnosis to consider?

Differential diagnosis will vary based on the duration, chronological sequence and anatomical localisation of symptoms and signs. Due to the non-specific nature of most brain tumour presentations, a range of different neurological conditions should be considered as alternative diagnoses or co-existent disorders. In patients with an established diagnosis of a primary headache disorder (e.g. tension-type headaches, migraines), a symptom diary can help to establish whether there has been a sufficient change in the frequency or characteristic of headache symptoms to warrant further investigation.

How to investigate?

If patients present with symptoms or signs of raised ICP (e.g. headache with papilloedema), refer them to the emergency department for same-day assessment and initial investigation with a contrast-enhanced CT head scan. If there is a history of possible new-onset seizure, arrange urgent referral to a specialist with expertise in epilepsy (e.g. a 'first fit' clinic) for confirmation of diagnosis and further investigations (e.g. contrast-enhanced MRI head, electroencephalogram) (31). For patients with a suspected brain tumour who do not display features suggestive of raised ICP or possible seizure activity, request an urgent MRI brain scan (including pre- and post-gadolinium contrast T1-weighted, T2-weighted, FLAIR and DWI sequences) (28,32), using a rapid-access 'suspected cancer' pathway, where available. In resource-limited settings, or in patients with contra-indications to MRI (e.g. non-MRI conditional devices, severe claustrophobia), a contrast-enhanced CT head scan is a less sensitive, but still valuable, alternative initial investigation.

The route of access to urgent neuroimaging varies by geographical region. In England, the National Institute for Health & Care Excellence (NICE) advise GPs to refer patients greater than 24 years of age with a 'progressive, sub-acute loss of central neurological function' for an urgent direct access MRI brain scan within 2 weeks (33). In contrast, NHS Scotland recommend an urgent referral to a specialist (e.g. neuro-oncologist) who subsequently arranges neuroimaging, if required (34). At time of referral, inform patients that they are being referred

in case they have cancer but also provide reassurance that the majority are not subsequently diagnosed with cancer (33).

Patients presenting with a suspected primary headache disorder and no high-risk features may still request a scan for reassurance that there is no serious underlying cause of their symptoms (35). This presents a significant dilemma for GPs who must balance the need to limit unnecessary investigations with their own concern about missing a brain tumour. Beside resource limitations, there are potential risks associated with neuroimaging which need to be considered (e.g. radiation exposure from CT scan, anaphylaxis from contrast agents) (36). Approximately 1 in every 37 MRI brain scans will also yield an incidental abnormality (37) which could require further specialist management or follow-up (e.g. aneurysm, arachnoid cyst, meningioma). While a reassuring scan can reduce service use for headaches in patients with high levels of psychological morbidity, it does not lead to lasting improvement in headache or anxiety symptoms (36). There is also a lack of evidence to suggest that earlier neuroimaging of patients with GBM who initially present with headaches would translate to any difference in clinical outcome. Patients without an indication for urgent neuroimaging should therefore be offered reassurance and encouraged to return if symptoms worsen or additional clinical features develop.

The classic MRI appearance of GBM is a mass lesion with peripheral contrast-enhancement on T1-weighted imaging (blood-brain barrier disruption), central hypointesity on T2-weighted images (necrosis) and surrounding hyper-intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images representing vasogenic oedema or infiltrating tumour [**Figure 2**] (38). Additional sequences such as diffusion-weighted imaging (DWI) can help to discriminate GBM from other contrast-enhancing mass lesions such as cerebral abscess or CNS lymphoma (38). Perfusion MRI and amino acid positron emission tomography (PET) scan imaging may be used to identify metabolic hotspots suitable for tissue sampling in patients undergoing biopsy as opposed to surgical resection (28).

How is it treated?

If imaging reveals a suspected brain tumour, refer the patient to a specialist neuro-oncology multi-disciplinary team (MDT) for confirmation of the diagnosis and further management [**Figure 3**] (32). For suspected GBM, first-line management is to offer maximal surgical resection for local tumour control prior to adjuvant treatment (28). In addition to obtaining

tissue for histopathological diagnosis, surgery aims to improve neurological function, facilitate steroid weaning, prolong survival and improve quality of life (28,39). In patients who are elderly, have a poor performance status or a tumour not amenable to surgical resection, the MDT may offer a less invasive biopsy procedure (28,32). If biopsy risk is considered too high or prognosis is likely to be very unfavourable, best supportive care alone or a short course of palliative radiotherapy is considered (28).

A recent systematic review and meta-analysis showed that greater extent of resection improved survival in patients with GBM (40). On the contrary, intra-operative injury to 'eloquent' brain tissue that is responsible for control of movement, sensation or speech, is associated with reduced quality of life and overall survival (41). To help maximise the extent of resection while minimising risk of post-operative disability various surgical adjuncts have been developed, including intra-operative neuroanatomical navigation systems, ultrasound, fluorescent dyes to visualise tumour tissue and cortical mapping in awake patients (28). Tumour specimens are classified and graded according to the WHO classification for CNS tumours, which was updated in 2016 to incorporate various molecular markers in addition to microscopic appearances (7,42). For GBM, an important genetic distinction is between tumours with and without mutations in genes encoding the metabolic enzyme isocitrate dehydrogenase (IDH). Despite similar histological appearances, IDH wild-type GBM has a more aggressive phenotype with a median survival of 15 months compared with 31 months in patients with an IDH-mutated GBM (43).

Following resection or biopsy, the additional treatment which is offered depends on age and performance status [**Figure 3**] (28,32). The standard treatment protocol for patients aged under 70 years who are capable of independent self-care (i.e. Karnofsky performance status ≥ 70) is daily fractionated radiation therapy over 6 weeks with concurrent and adjuvant temozolomide, an oral alkylating chemotherapy, for a maximum of 6 months (2,28,32). Older patients with a similar performance status can be offered an abbreviated course of hypofractionated radiotherapy with concurrent and adjuvant temozolomide for up to 12 months (28,32,44). In patients with IDH wild-type glioblastoma, response to temozolomide chemotherapy can be predicted by the promoter methylation status of the O^6-methylguanine DNA methyltransferase (MGMT) gene which encodes a DNA repair enzyme known to antagonise the effect of alkylating chemotherapy (42). Epigenetic silencing in MGMT promoter-methylated tumours therefore confers heightened response to temozolomide and

improved survival, with only marginal effects in MGMT promoter-unmethylated tumours (28,42).

What is the prognosis?

In adults aged under 70 years who do not undergo surgery, median survival is approximately 3-4.5 months (3,45). A biopsy procedure followed by chemotherapy, with or without radiotherapy, improves median survival to 8-10 months (2,3,45). Maximal treatment with debulking surgery followed by chemoradiotherapy is associated with the longest median survival of around 15-16 months (2,3,45).

Elderly patients who receive best supportive care alone are expected to have a median survival of less than 4 months (1). In patients aged over 65 years who have undergone biopsy or resection, hypofractionated radiotherapy and chemotherapy improve median survival from 7 to 9 months, compared with radiation alone (44). Despite evidence of a survival advantage, addition of adjuvant chemotherapy does not improve quality of life in this group (44). Due to the incurable nature of GBM, patients should be appropriately counselled about the potential impact of adverse effects of treatments on quality of life and not only potential survival benefits, especially in elderly patients and those with a poor performance status who have a particularly poor prognosis.

What supportive medication may be required?

Corticosteroids: The vast majority of patients with GBM receive corticosteroids during the course of their disease. This can relieve headache, nausea and vomiting by reducing peritumoral vasogenic oedema and mass effect (23). Dexamethasone is the preferred choice and can be commenced prior to surgery unless there is a suspicion of primary cerebral lymphoma or an inflammatory CNS lesion as steroids can confound diagnosis in this setting (28). There is no consensus on optimal dosing and steroid requirements vary according to tumour size, location, peritumoral oedema and symptoms. Since patients with GBM can often remain on steroids for several months, they are at increased risk of the long-term side effects of steroids [**Table 1**]. Steroid-induced hyperglycaemia is a common adverse effect which can not only exacerbate hyperglycaemia in patients with known diabetes mellitus (DM), but also may lead to the onset of DM in patients without a prior history of the condition (46). The aim should be to use steroids for a short period of time and, if patients remain symptomatic, to taper to the lowest possible maintenance dose that controls symptoms. Gastric protection with

proton-pump inhibitor or H_2-receptor antagonist is recommended for patients taking regular corticosteroids.

Anti-epileptic drugs (AEDs): AEDs are recommended for patients who have had a seizure, but there is no good-quality evidence to support their prophylactic use (11,28,47,48). National clinical guidelines recommend choice of formulation based on various factors, including age and seizure type (31,51). Non-enzyme inducing AEDs are preferred to avoid interactions with chemotherapy and steroids (48). Some AEDs may lack efficacy in patients with GBM due to loss or receptor sensitivity or expression of multidrug-resistance proteins, which can result in refractory epilepsy (49,50). Levetiracetam is often the first drug of choice in most neuro-oncology centres [**Table 1**] since it is usually well-tolerated, can be initiated orally at a therapeutic dose, does not require monitoring and is not thought to be affected multi-drug resistance proteins (23,48–50). There is no consensus regarding the optimal duration of AED therapy in GBM patients and many clinicians therefore opt to continue AEDs indefinitely if they are well tolerated (51). Any decision to discontinue AEDs should take into account seizure history, tumour residual, anticipated tumour growth, medication side effects and patient preference (51).

Venous thromboembolism (VTE): Patients with GBM are at increased risk of VTE in the peri-operative period and beyond, with a 1 year incidence of around 20% (52). A large randomised, double-blind study in post-operative elective neurosurgery inpatients, most of whom had brain tumours, showed that prophylactic low molecular weight heparin (LMWH) was effective in reducing the rate of VTE without increasing the risk of haemorrhagic complications (53). There is, however, no good-quality evidence to support the use of continuing prophylactic LMWH on discharge (11,23). If patients with GBM develop VTE, therapeutic anticoagulation is generally considered safe, unless there has been recent haemorrhage from the tumour or chemotherapy-related thrombocytopenia (11,54). There is currently no consensus on the preferred choice of anticoagulant or duration of treatment in this patient group.

Cognitive and mood disturbances: Approximately 9 in 10 patients with brain tumours display cognitive deficits before commencing treatment (55). This is likely to be exacerbated by cancer-related fatigue and sleep disturbance (11). Randomised controlled trials (RCTs) to date have failed to show a beneficial effect of acetylcholinesterase inhibitors or psychostimulants in overall rates of cognitive decline or symptoms of fatigue in this group (11,54). Depression

can affect 1 in 5 patients with glioma (56). No RCTs to date have investigated the efficacy of pharmacological treatments for depression in this patient group (57).

What advice should be given on driving?

Inform patients with a new diagnosis of GBM that they must not drive and must notify the driver licensing authority of their condition. Following treatment, the judgement on whether a patient has the competency to start driving again is not only based on history of epileptic seizure, but also the presence of any neurological or cognitive deficits (48).

How are patients followed-up?

Follow-up is usually co-ordinated by a neuro-oncologist and is an opportunity to monitor the physical and psychological wellbeing of patients and caregivers. For patients receiving adjuvant temozolomide, a full blood count is performed weekly due to risk of myelosuppression, with addition of monthly renal and liver function tests. If the tumour is located close to the hypothalamus or pituitary, endocrine tests to monitor hypothalamic-pituitary axis function are recommended (58). Repeat neuroimaging is critical in establishing response to treatment and monitoring for disease recurrence. A baseline gadolinium-enhanced MRI brain scan is performed 24-48 hours following surgery(28). This is usually compared with a repeat MRI scan 1-2 months after completion of radiotherapy to determine initial response to treatment. The subsequent schedule for clinical reviews and follow-up imaging is usually at 3 monthly intervals or sooner dependent upon the volume of residual tumour, response to treatment, patient preference and life expectancy (32).

If a patient develops worsening headaches or a new focal neurological deficit before their next review, arrange an urgent clinical assessment to determine if a repeat MRI (or CT) scan is required (32).

How is disease recurrence managed?

In spite of surgical resection and chemoradiotherapy, GBM invariably recurs (59). Up to 80% of tumour recurrences are within 2 cm of the initial tumor site; the remainder arise in distant brain regions, suggesting microscopic invasion of tumour cells beyond the original resection margin (59,60). Recurrent GBM is frequently more aggressive and less treatment-responsive than the initial tumour (59). Further treatment options are at the discretion of the specialist neuro-oncology MDT who take into account tumour phenotype, time since last treatment,

patient preference and performance status (32). If there is focal recurrence of disease, repeat surgical resection is an option (32). Further radiotherapy can also be considered depending on the time since original treatment and location of disease (32). Early randomised trial results suggest this approach could prolong progression-free survival without an overall survival benefit (61). If further chemotherapy is considered, options include lomustine, or combination therapy with procarbazine, lomustine and vincristine (PCV) (32). Inclusion into a clinical trial can also be considered (28). If a patient does not wish to receive further treatment, or additional disease-modifying therapy is unlikely to be of clinical benefit, an active palliative care approach is favoured (32).

What is the typical illness experience of patients with GBM and their carers?

Patients with GBM have been found to have archetypical trajectories of physical, social, psychological and existential distress which start even before a diagnosis is confirmed (62). Social decline may follow a similar pattern to that of physical decline, whereas psychological and existential distress are typically acute at 4 stages: around diagnosis, after initial treatment, at disease progression and at the end of life. We define existential or spiritual issues as relating to the meaning and purpose of life (63). Each patient's individual course varies according to other factors including co-morbidities and the availability of individual family and community resources (e.g., personal resilience and emotional support). As previously described with progressive lung cancer (64), patients and family carers of patients with GBM may follow a roller-coaster experience as they experience worry and distress [**Figure 4**].

Understanding these typical illness experiences allows health and social care professionals to predict their patients' and carers' likely needs so they can provide appropriate support and sensitive and effective communication from before diagnosis to bereavement support to the carer. [**Box 3**]. Early provision of a palliative care approach by GPs and hospital clinicians, not just by palliative care specialists, can have a significant impact in improving the quality of life and death of patients and carers affected by GBM diagnosis.

BOX 1: High-risk features of headaches associated with brain tumours*

- Headache triggered by cough, valsalva, sneeze or exercise
- Orthostatic headache (exacerbated by supine position)
- A substantial change in headache characteristics
- Associated with new-onset neurological deficit, change in personality or cognitive dysfunction
- Impaired level of consciousness
- Vomiting without other obvious cause
- History of malignancy known to metastasise to brain

**Adapted from NICE Clinical Guideline CG150 - Headaches in over 12s: diagnosis and management (65)*

BOX 2: The carer's perspective

Our lives were shattered when he suddenly experienced a terrifying grand mal seizure. He was rushed to A&E and kept in for numerous tests. The consultant informed him in a very matter-of-fact manner that he had a brain tumour. It was before visiting hours, so he was on his own when he was given this devastating news. Looking back, he had always had headaches for as long as I had known him. Before the seizure, he had been quite tired and was having afternoon naps. He had also vomited once, but we thought it might be an upset stomach.

He was referred a neurosurgeon and underwent a resection craniotomy. Unfortunately, a few days later we received the crushing news that it was a glioblastoma with a prognosis of less than 15 months. One of the biggest blows, was being told that he could not drive again. Losing his licence meant losing his independence. He started 6 weeks of daily radiotherapy, followed by 12 months of chemotherapy. He realized early on that by simply following the standard treatment plan, he was not going to live life to the full. Learning about diet, exercise, wellbeing, relationships, resilience and managing stress had a huge impact on his state of mind. When he became bed-bound, community nurses would visit our home to wash and dress him. I do not know what I would have done without them. Staff at the hospice were so kind and compassionate, and allowed me to stay every day and night. It was the first time since his diagnosis that I felt I could be his wife, and not just his carer.

If I were to share our experience with doctors, I would say please always be empathic. For example, when he first started taking dexamethasone and stopped sleeping at night and became agitated, I thought he had changed forever. It would have been helpful to know that these changes might happen and that they would be temporary.

The most important thing for a patient is to feel that they have some sort of control of their lives, no matter what their prognosis.

BOX 3: Practical suggestions for clinicians caring for patients with GBM and their caregivers

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On referral:

- acknowledge that uncertainty while awaiting diagnosis can be distressing

Around diagnosis:

- offer further information about the diagnosis and what will likely happen next
- signpost to relevant organisations such as brain cancer charities that offer support

During initial treatment:

- listen to and explore any problems or questions that the patient may have
- offer supportive advice to caregivers and allow them to ask questions
- facilitate prompt communication between primary care and hospital teams

At follow-up visits with specialist or general practitioner:

- identify a named contact (e.g. specialist nurse or family physician) who can offer psycho-social support and practical advice
- discuss what the future may hold, and together document a care plan and send a summary electronically to all settings including urgent and emergency care
- engage caregivers in discussions about what practical assistance may be helpful

Disease progression

- offer patients the opportunity to review their future care plan, including sensitive discussion of their resuscitation preferences, and preferred place of death
- seek patient consent to involve caregivers in discussions about end-of-life care
- regularly communicate the revised care plan with all involved, including out-of-hours services
- stay in contact and establish if additional support is required

Bereavement

- offer an initial bereavement visit from a known healthcare professional
- arrange further support for caregiver and family as required

Other article boxes

Source & selection criteria

We searched PubMed using the terms “Glioblastoma”, “Glioma” or “Astrocytoma”. We also hand-searched reference lists of included papers. In addition, for clinical guidelines we searched the websites of the National Institute for Health & Care Excellence (NICE), the European Association of Neuro-Oncology (EANO) and BMJ Best Practice. We reference and draw conclusions from large cohort studies, randomised clinical trials and systematic reviews with or without meta-analysis.

Information resources for patients

- Macmillan Cancer Support (https://www.macmillan.org.uk/) - Offers support to patients diagnosed with any cancer in the UK
- Brainstrust charity (https://brainstrust.org.uk) - Offers specialist support to patients diagnosed with brain tumours in the UK
- Marie Curie charity (https://www.mariecurie.org.uk) - Offers care and support to patients with terminal illnesses and their families. Provides advice on advance care planning.

Education into practice

- What symptoms and signs would make you consider a possible diagnosis of a brain tumour?
- How are patients with suspected brain tumours initially investigated?
- What is the current standard treatment of glioblastoma in adult patients?
- Think about the last time you reviewed a patient with brain cancer. Did you inquire about caregiver wellbeing and establish if they require additional support?

Questions for future research

- Are there any biomarkers which could expedite GBM diagnosis and monitor treatment response?
- What interventions can shorten the time to diagnosis and do these affect survival outcome?
- How can clinical trial design be adapted to examine the efficacy of future targeted drug therapies?

How patients were involved in the creation of this article

We invited a caregiver to write a personal account of their partner's glioblastoma diagnosis and treatment, as well as to comment on what they felt doctors reading this article should know [**Box 2**]. In addition, we invited a representative of the brain tumour community to comment on the manuscript. They added some practical suggestions for clinicians caring for patients with glioma and their caregivers [**Box 3**], as well as making textual edits to the manuscript. We are grateful for their input.

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Contributorship statement

CM developed the idea for the article, co-designed the structure and content, performed the literature search and wrote the first draft of the manuscript. He is guarantor for the article. PP co-designed the structure and content of the article, and supervised the work. MN, SAM and PP contributed individually to the writing of the final draft, sharing expertise from their own disciplines. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

References

1. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: State of the art and future directions. CA: A Cancer Journal for Clinicians. 2020;70(4):299–312.

2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987–96.

3. Brodbelt A, Greenberg D, Winters T, Williams M, Vernon S, Collins VP. Glioblastoma in England: 2007–2011. European Journal of Cancer. 2015 Mar 1;51(4):533–42.

4. Larjavaara S, Mäntylä R, Salminen T, Haapasalo H, Raitanen J, Jääskeläinen J, et al. Incidence of gliomas by anatomic location. Neuro Oncol. 2007 Jul;9(3):319–25.

5. Gállego Pérez-Larraya J, Hildebrand J. Brain metastases. Handb Clin Neurol. 2014;121:1143–57.

6. Lapointe S, Perry A, Butowski NA. Primary brain tumours in adults. The Lancet. 2018 Aug 4;392(10145):432–46.

7. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016 Jun 1;131(6):803–20.

8. Aldape K, Zadeh G, Mansouri S, Reifenberger G, von Deimling A. Glioblastoma: pathology, molecular mechanisms and markers. Acta Neuropathol. 2015 Jun 1;129(6):829–48.

9. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro Oncol. 2018 01;20(suppl_4):iv1–86.

10. Thakkar JP, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and Molecular Prognostic Review of Glioblastoma. Cancer Epidemiol Biomarkers Prev. 2014 Oct;23(10):1985–96.

11. Wen PY, Weller M, Lee EQ, Alexander BM, Barnholtz-Sloan JS, Barthel FP, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol. 2020 Aug 17;22(8):1073–113.

12. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a “state of the science” review. Neuro Oncol. 2014 Jul 1;16(7):896–913.

13. Ostrom QT, Adel Fahmideh M, Cote DJ, Muskens IS, Schraw JM, Scheurer ME, et al. Risk factors for childhood and adult primary brain tumors. Neuro Oncol. 2019 Nov 4;21(11):1357–75.

14. Routes to diagnosis [Internet]. [cited 2020 Oct 23]. Available from: http://www.ncin.org.uk/publications/routes_to_diagnosis

15. Lyratzopoulos G, Abel GA, McPhail S, Neal RD, Rubin GP. Measures of promptness of cancer diagnosis in primary care: secondary analysis of national audit data on patients with 18 common and rarer cancers. Br J Cancer. 2013 Feb 19;108(3):686–90.

16. Walter FM, Penfold C, Joannides A, Saji S, Johnson M, Watts C, et al. Missed opportunities for diagnosing brain tumours in primary care: a qualitative study of patient experiences. Br J Gen Pract. 2019 Apr 1;69(681):e224–35.

17. HeadSmart Be Brain Tumour Aware. A new clinical guideline from the Royal College of Paediatrics and

Child Health with a national awareness campaign accelerates brain tumor diagnosis in UK children--"HeadSmart: Be Brain Tumour Aware". Neuro Oncol. 2016 Mar;18(3):445–54.

18. Ozawa M, Brennan PM, Zienius K, Kurian KM, Hollingworth W, Weller D, et al. The usefulness of symptoms alone or combined for general practitioners in considering the diagnosis of a brain tumour: a case-control study using the clinical practice research database (CPRD) (2000-2014). BMJ Open. 2019 Aug 1;9(8):e029686.

19. Hamilton W, Kernick D. Clinical features of primary brain tumours: a case-control study using electronic primary care records. Br J Gen Pract. 2007 Sep;57(542):695–9.

20. Kernick D, Stapley S, Goadsby PJ, Hamilton W. What happens to new-onset headache presented to primary care? A case-cohort study using electronic primary care records. Cephalalgia. 2008 Nov;28(11):1188–95.

21. Valentinis L, Tuniz F, Valent F, Mucchiut M, Little D, Skrap M, et al. Headache attributed to intracranial tumours: a prospective cohort study. Cephalalgia. 2010 Apr;30(4):389–98.

22. Kirby S, Purdy RA. Headaches and Brain Tumors. Neurologic Clinics. 2014 May 1;32(2):423–32.

23. Schiff D, Lee EQ, Nayak L, Norden AD, Reardon DA, Wen PY. Medical management of brain tumors and the sequelae of treatment. Neuro Oncol. 2015 Apr;17(4):488–504.

24. Rasmussen BK, Hansen S, Laursen RJ, Kosteljanetz M, Schultz H, Nørgård BM, et al. Epidemiology of glioma: clinical characteristics, symptoms, and predictors of glioma patients grade I–IV in the the Danish Neuro-Oncology Registry. J Neurooncol. 2017 Dec 1;135(3):571–9.

25. Posti JP, Bori M, Kauko T, Sankinen M, Nordberg J, Rahi M, et al. Presenting symptoms of glioma in adults. Acta Neurol Scand. 2015 Feb;131(2):88–93.

26. Penfold C, Joannides AJ, Bell J, Walter FM. Diagnosing adult primary brain tumours: can we do better? Br J Gen Pract. 2017 Jun 1;67(659):278–9.

27. Improving outcomes for people with brain and other central nervous system tumours | Guidance | NICE [Internet]. NICE; [cited 2020 Oct 21]. Available from: https://www.nice.org.uk/guidance/csg10

28. Weller M, van den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021 Mar;18(3):170–86.

29. Robinson GA, Biggs V, Walker DG. Cognitive Screening in Brain Tumors: Short but Sensitive Enough? Front Oncol [Internet]. 2015 [cited 2021 May 2];5. Available from: https://www.frontiersin.org/articles/10.3389/fonc.2015.00060/full

30. van Kessel E, Baumfalk AE, van Zandvoort MJE, Robe PA, Snijders TJ. Tumor-related neurocognitive dysfunction in patients with diffuse glioma: a systematic review of neurocognitive functioning prior to anti-tumor treatment. J Neurooncol. 2017;134(1):9–18.

31. Overview | Epilepsies: diagnosis and management | Guidance | NICE [Internet]. NICE; [cited 2021 May 2]. Available from: https://www.nice.org.uk/guidance/cg137

32. Overview | Brain tumours (primary) and brain metastases in adults | Guidance | NICE [Internet]. NICE; [cited 2020 Oct 21]. Available from: https://www.nice.org.uk/guidance/NG99

33. Overview | Suspected cancer: recognition and referral | Guidance | NICE [Internet]. NICE; [cited 2020 Oct 21]. Available from: https://www.nice.org.uk/guidance/ng12

34. Brain and Central Nervous System Cancers [Internet]. NHS Scotland Primary Care Cancer Referral

Guidelines. [cited 2020 Nov 5]. Available from: http://www.cancerreferral.scot.nhs.uk

35. Morgan M, Jenkins L, Ridsdale L. Patient pressure for referral for headache: a qualitative study of GPs'referral behaviour. Br J Gen Pract. 2007 Jan 1;57(534):29–35.

36. Howard L, Wessely S, Leese M, Page L, McCrone P, Husain K, et al. Are investigations anxiolytic or anxiogenic? A randomised controlled trial of neuroimaging to provide reassurance in chronic daily headache. Journal of Neurology, Neurosurgery & Psychiatry. 2005 Nov 1;76(11):1558–64.

37. Morris Z, Whiteley WN, Longstreth WT, Weber F, Lee Y-C, Tsushima Y, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. BMJ. 2009 Aug 17;339:b3016.

38. Wirsching H-G, Galanis E, Weller M. Glioblastoma. Handb Clin Neurol. 2016;134:381–97.

39. Sagberg LM, Solheim O, Jakola AS. Quality of survival the 1st year with glioblastoma: a longitudinal study of patient-reported quality of life. Journal of Neurosurgery. 2016 Apr 1;124(4):989–97.

40. Brown TJ, Brennan MC, Li M, Church EW, Brandmeir NJ, Rakszawski KL, et al. Association of the Extent of Resection With Survival in Glioblastoma. JAMA Oncol. 2016 Nov 1;2(11):1460–9.

41. Jakola AS, Gulati S, Weber C, Unsgård G, Solheim O. Postoperative Deterioration in Health Related Quality of Life as Predictor for Survival in Patients with Glioblastoma: A Prospective Study. PLOS ONE. 2011 Dec 9;6(12):e28592.

42. Reifenberger G, Wirsching H-G, Knobbe-Thomsen CB, Weller M. Advances in the molecular genetics of gliomas - implications for classification and therapy. Nat Rev Clin Oncol. 2017 Jul;14(7):434–52.

43. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, et al. IDH1 and IDH2 Mutations in Gliomas. New England Journal of Medicine. 2009 Feb 19;360(8):765–73.

44. Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma [Internet]. http://dx.doi.org/10.1056/NEJMoa1611977. 2017 [cited 2019 Sep 17]. Available from: https://www.nejm.org/doi/10.1056/NEJMoa1611977

45. Bjorland LS, Fluge O, Gilje B, Mahesparan R, Farbu E. Treatment approach and survival from glioblastoma: results from a population-based retrospective cohort study from Western Norway. BMJ Open. 2021 Mar 1;11(3):e043208.

46. Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. World J Diabetes. 2015 Jul 25;6(8):1073–81.

47. Greenhalgh J, Weston J, Dundar Y, Nevitt SJ, Marson AG. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. Cochrane Database Syst Rev. 2020 28;4:CD007286.

48. Roth P, Pace A, Le Rhun E, Weller M, Ay C, Cohen-Jonathan Moyal E, et al. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up. Ann Oncol. 2021 Feb;32(2):171–82.

49. van Breemen MS, Wilms EB, Vecht CJ. Epilepsy in patients with brain tumours: epidemiology, mechanisms, and management. The Lancet Neurology. 2007 May 1;6(5):421–30.

50. Van Breemen MSM, Wilms EB, Vecht CJ. Chapter 26 - Seizure control in brain tumors. In: Aminoff MJ, Boller F, Swaab DF, editors. Handbook of Clinical Neurology [Internet]. Elsevier; 2012 [cited 2021 May 13]. p. 381–9. (Neuro-Oncology; vol. 104). Available from: https://www.sciencedirect.com/science/article/pii/B9780444521385000268

51. Armstrong TS, Grant R, Gilbert MR, Lee JW, Norden AD. Epilepsy in glioma patients: mechanisms, management, and impact of anticonvulsant therapy. Neuro Oncol. 2016 Jun;18(6):779–89.

52. Czap AL, Becker A, Wen PY. Thrombotic Complications in Gliomas. Semin Thromb Hemost. 2019 Jun;45(4):326–33.

53. Agnelli G, Piovella F, Buoncristiani P, Severi P, Pini M, D'Angelo A, et al. Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med. 1998 Jul 9;339(2):80–5.

54. Pace A, Dirven L, Koekkoek JAF, Golla H, Fleming J, Rudà R, et al. European Association for Neuro-Oncology (EANO) guidelines for palliative care in adults with glioma. The Lancet Oncology. 2017 Jun 1;18(6):e330–40.

55. Tucha O, Smely C, Preier M, Lange KW. Cognitive deficits before treatment among patients with brain tumors. Neurosurgery. 2000 Aug;47(2):324–33; discussion 333-334.

56. Rooney AG, McNamara S, Mackinnon M, Fraser M, Rampling R, Carson A, et al. Frequency, clinical associations, and longitudinal course of major depressive disorder in adults with cerebral glioma. J Clin Oncol. 2011 Nov 10;29(32):4307–12.

57. Rooney A, Grant R. Pharmacological treatment of depression in patients with a primary brain tumour. Cochrane Database Syst Rev. 2013 May 31;(5):CD006932.

58. Astrocytic brain tumours - Monitoring | BMJ Best Practice [Internet]. [cited 2020 Nov 5]. Available from: https://bestpractice.bmj.com/topics/en-gb/729/monitoring

59. Campos B, Olsen LR, Urup T, Poulsen HS. A comprehensive profile of recurrent glioblastoma. Oncogene. 2016 Nov;35(45):5819–25.

60. Brandes AA, Tosoni A, Franceschi E, Sotti G, Frezza G, Amistà P, et al. Recurrence Pattern After Temozolomide Concomitant With and Adjuvant to Radiotherapy in Newly Diagnosed Patients With Glioblastoma: Correlation With MGMT Promoter Methylation Status. JCO. 2009 Feb 2;27(8):1275–9.

61. Tsien C, Pugh S, Dicker adam, Raizer J, Matuszak M, Lallana E, et al. ACTR-32. NRG ONCOLOGY RTOG 1205: RANDOMIZED PHASE II TRIAL OF CONCURRENT BEVACIZUMAB AND RE-IRRADIATION VS. BEVACIZUMAB ALONE AS TREATMENT FOR RECURRENT GLIOBLASTOMA. Neuro-Oncology. 2019 Nov 11;21(Supplement_6):vi20–vi20.

62. Cavers D, Hacking B, Erridge SE, Kendall M, Morris PG, Murray SA. Social, psychological and existential well-being in patients with glioma and their caregivers: a qualitative study. CMAJ. 2012 Apr 17;184(7):E373–82.

63. Murray SA, Kendall M, Boyd K, Worth A, Benton TF. Exploring the spiritual needs of people dying of lung cancer or heart failure: a prospective qualitative interview study of patients and their carers. Palliat Med. 2004 Jan 1;18(1):39–45.

64. Murray SA, Kendall M, Boyd K, Grant L, Highet G, Sheikh A. Archetypal trajectories of social, psychological, and spiritual wellbeing and distress in family care givers of patients with lung cancer: secondary analysis of serial qualitative interviews. BMJ [Internet]. 2010 Jun 10 [cited 2020 Nov 26];340. Available from: https://www.bmj.com/content/340/bmj.c2581

65. Recommendations | Headaches in over 12s: diagnosis and management | Guidance | NICE [Internet]. NICE; [cited 2021 May 2]. Available from: https://www.nice.org.uk/guidance/cg150/chapter/recommendations#diagnosis

Figure legends

Fig 1: Frequency of symptoms reported to general practitioners in 6 months prior to brain tumour diagnosis. Adapted from Ozawa M et al, 2019. (18)

Fig 2: Axial MRI head scan with (A) gadolinium-enhanced T1-weighted, (B) T2-weighted and (C) FLAIR sequences demonstrating a right parietal glioblastoma.

Fig 3: Glioblastoma management pathway. Adapted from NICE guideline NG99 (2018) (32). †Consider biopsy if surgical resection not considered possible (e.g. poor performance status). ††Consider if histopathological diagnosis cannot be made due to high risk of biopsy or very unfavourable prognosis (28).

Fig 4: Typical fluctuations in trajectories of physical, social, psychological and spiritual wellbeing in patients with GBM and their family carers. Adapted from Murray et al., 2010 (64).