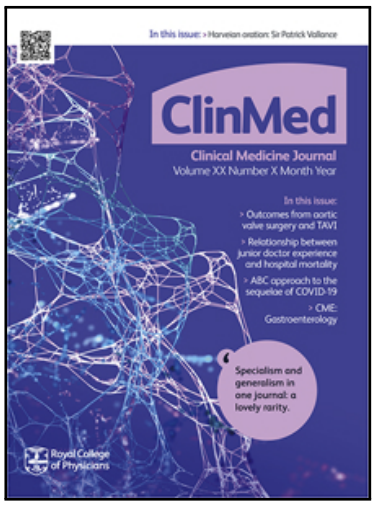

Gliomas in adults: Guidance on Investigations, Diagnosis, Treatment & Surveillance

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Abstract

Primary brain tumours are rare but carry a significant morbidity and mortality burden. Malignant gliomas are the most common subtype and their incidence is increasing within our ageing population. The diagnosis and treatment of gliomas involves substantial interplay between multiple specialities, including general medical physicians, radiologists, pathologists, surgeons, oncologists and allied health professionals. At any point along this pathway patients can present to acute medicine with complications of their cancer or anti-cancer therapy. Increasing the awareness of malignant gliomas amongst general physicians is paramount to delivering prompt radiological and histopathological diagnoses, facilitating access to earlier and individualised treatment options and allows for effective recognition and management of anticipated complications. This article discusses evidence-based real-world practice for malignant gliomas, encompassing patient presentation, diagnostic pathways, treatments and their complications, and prognosis to guide management outside of specialist centres.

Keywords:

Glioma; Presentation; Diagnosis; Management; Complications

Introduction

Primary brain tumours are rare but carry a significant morbidity and mortality burden. They represent a disparate group of tumours that can be benign or malignant. Malignant primary brain tumours account for 3% of total UK cancer cases, with approximately 12, 000 new cases in the UK/year, and roughly 80% of these are classified as diffuse gliomas.[1,2] Although gliomas can occur during childhood, the risk increases with age for most subtypes. Less than 2% are related to modifiable risk factors including obesity and ionising radiation.[1] Given that many patients with glioma present through acute medical services with complications of their cancer or treatment, an understanding of gliomas is essential for all general medical physicians. This review provides an overview to help guide the initial investigation and management pathway outside of neuro-oncology hospitals.

Histological classification of adult gliomas

Assessment of tumours by histology and immunohistochemistry (IHC) is a vital first step in diagnosis, and diffuse adult gliomas can usually be described as having an oligodendroglial or astrocytic morphology. Molecular tests should be performed to refine the differential diagnosis suggested by morphological assessment.[3] Broadly, adult gliomas can be categorised into IDH-mutant or IDH-wildtype tumours (Figure 1).

The most common IDH wildtype glioma is glioblastoma, CNS WHO grade 4. These tumours have an astrocytic morphology and display high-grade morphological features including necrosis and/or microvascular proliferation.

There are two astrocytic gliomas with defining histone alterations, which usually present with high-grade histology, with characteristic anatomical locations and presentation predominantly in childhood, adolescence or young adulthood: diffuse midline glioma, H3 K27–altered and diffuse hemispheric glioma, H3 G34-mutant. Both of these are CNS WHO grade 4 tumours.

Mutations of *IDH1/2* genes are the defining molecular alteration in astrocytomas and oligodendrogliomas.

Astrocytomas will also commonly harbour *TP53* and ATRX mutations, with loss of nuclear expression of ATRX on IHC, but will not have chromosome 1p/19q codeletion. Astrocytoma, IDH-mutant is now stratified into CNS WHO grades 2, 3 or 4 based on degree of proliferation, presence of anaplasia or necrosis or CDKN2A/B deletion. Previously, the term ‘glioblastoma, IDH-mutant’ was used, however it is now recognised that astrocytoma IDH-mutant, CNS WHO grade 4 is a biologically distinct entity from glioblastoma.

Oligodendrogliomas are defined as IDH-mutant gliomas with 1p/19q codeletion and will also commonly have a *TERT* promoter mutation. They are stratified into CNS WHO grade 2 or 3 tumours based on proliferation and anaplasia.

Testing for methylation of the *MGMT* promoter should be performed in the setting of diffuse gliomas as it is a predictive biomarker for response to alkylating chemotherapy (Temozolomide).

As molecular features gain prominence in the diagnostic criteria for brain tumours, array-based DNA methylation profiling and next generation sequencing approaches are frequently used for refinement or confirmation of diagnosis in histologically difficult cases, for prognostication and for the identification of defining or potentially actionable molecular alterations.

Presentation

Although gliomas can present at any age, the incidence of low-grade gliomas peaks between the age of 35 to 45 whereas high grade gliomas typically present in the 7th and 8th decades of life. Presenting signs and symptoms can be secondary to raised intracranial pressure or the tumour itself. Seizures are a common presentation. Other symptoms can include headaches, focal neurological deficit, visual field defects, confusion, emesis and papilloedema. Raised intracranial pressure is more commonly seen in high grade gliomas complicated by blood-brain barrier disruption and vasogenic oedema.[4,5] Lobar specific presentations, such as temporal lobe epilepsy with olfactory and gustatory seizures, must be carefully elucidated in history taking. Receptive and expressive dysphasia can indicate frontal or temporal lobe tumours, whereas occipitally based tumours can produce specific visual field defects. Red flag features that warrant urgent neuro-investigation include a progressive deterioration in higher neurological function, new or progressive headache with associated focal neurology or an atypical symptomatology, papilloedema on fundoscopy, or a new presentation with seizures.[6,7]

Initial Investigation

Investigations should include an ophthalmological evaluation, routine haemato-biochemistry, and imaging of the brain. Although computed tomography (CT) may be used in the acute setting, magnetic resonance imaging (MRI) with administration of gadolinium-based contrast is the definitive imaging examination for brain tumour diagnosis. Where intracranial metastases are in the

differential a CT scan of the chest, abdomen and pelvis, in addition to a clinical exam (particularly skin/breast) should also be performed.

Diagnostic Imaging

A recommended protocol for brain MRI scans is included in Table 1, which includes structural sequences for delineation of anatomy and to help with operative and radiotherapy planning, and advanced sequences (Diffusion weighted imaging (DWI), Susceptibility weighted imaging (SWI), perfusion, and spectroscopy) which can provide information about the grade as well as distinguish tumour from tumour mimics (Figure 2).[8]

Low-grade diffuse gliomas typically appear as expansile signal abnormality, best demonstrated on T2 or FLAIR sequences, without contrast enhancement. This non-enhancing tumour can be mimicked by acute infarct or encephalitis on MRI. Oligodendrogliomas may demonstrate calcification, seen on CT or on SWI, and may demonstrate contrast enhancement and increased perfusion even if low-grade, whereas IDH-mutant astrocytomas are more likely to demonstrate internal decreased FLAIR hyperintensity (T2-FLAIR mismatch sign).[9] Features more associated with high-grade gliomas include contrast enhancement, necrosis (a peripheral pattern of contrast enhancement), haemorrhage (best seen on SWI) and increased cerebral blood volume on perfusion imaging, and can sometimes show different features on spectroscopy.[10] These patterns are also used to assess for transformation of tumours during surveillance. Mimics of high grade gliomas include lymphoma, which tends to have a more solidly enhancing appearance with diffusion restriction (Figure 2) although can be more heterogeneous in immunosuppressed patients; metastases, which are more likely to be multiple and located at the corticomedullary junction; and abscess, which tends to demonstrate internal diffusion restriction and smooth peripheral enhancement (compared to the peripheral diffusion restriction that can be seen with high grade astrocytomas).

Assessment

All patients with intracranial space occupying lesions should be referred for initial discussion at a Neuro-Oncology multi-disciplinary team (MDT) meeting. Treatment decisions are based on tumour type and grade, location and a patient's current physical and functional status. Useful scales for measuring patient fitness are the ECOG or Karnofsky Performance Status. However, these are relatively crude tools and there is increasing interest in using frailty scores or geriatric assessment techniques in older patients.[11] Specific cognitive deficits are often not highlighted in routine assessments therefore the use of the Neurologic Assessment in Neuro Oncology scale is

recommended alongside baseline cognitive and speech assessments using the Montreal Cognitive Assessment Scale or the MMSE, ideally in conjunction with a speech and language therapist.[12]

Patients should be informed that a diagnosis of an intracranial malignancy means they are not allowed to drive with immediate effect, and they should inform the DVLA. The DVLA then has criteria of when they may regain their license depending on the grade of tumour, subsequent treatment received and any associated seizure activity.

Treatment options can include surveillance, surgery, radiotherapy, chemotherapy and best supportive care. Enrolment in clinical trials should always be considered.

Surgical treatment

Surgical resection represents the standard of care in the majority of gliomas for both tissue diagnosis and the alleviation of pressure symptoms. The option of an image guided biopsy for molecular classification is usually indicated for tumours with unfavourable anatomical location where the risk of permanent severe functional deficits from resecting the tumour is unacceptably high. Neuronavigation platforms establish the spatial relationship between the patient's head and the pre-operative imaging, optimising the trajectory to the lesion to improve outcomes. Intraoperative brain shift is often a limitation in using navigation as a tool to assess resection; this limitation can be complemented with intraoperative imaging.

The concept of maximal safe resection has evolved over the last two decades into the standard of care. It represents a balance between maximising the extent of resection and minimising permanent neurological deficits that affect quality of life. Mounting evidence supports an association between greater surgical resection and longer life expectancy for both high-grade and low-grade gliomas, although definitive class I evidence is lacking.[13,14]

There are a number of surgical techniques and technological adjuncts currently available to the Neurosurgeon for the treatment of gliomas. For pre-surgical planning in eloquent areas, tractography (DTI), functional MRI (fMRI) and image guidance have increasingly become standard. Intra-operative imaging with ultrasound or intra-operative MRI are gaining popularity. Intraoperative pathological diagnosis using frozen section or other techniques such as squash smear cytology or intraoperative confocal laser microscopy are innovative tools to help guide the extent of resection; tumour boundaries, especially when high grade, can often be unclear. The use of 5-ALA or sodium fluorescence-guided surgery has resulted in increased rates of complete resections of high-grade gliomas and better outcomes than with conventional microsurgery.[15]

Surgery for gliomas can be performed with patients asleep or awake. Awake craniotomy can help identify and preserve functional areas during cortical and subcortical tumour resections.[16] The rationale is to maximise resection whilst preserving the "onco-functional balance" at an individual level.[17] It is associated with extremely low complication and failure rates, regardless of ASA classification, tumour location, dimensions, and pathology.[16]

Intraoperative mapping is fundamental to achieving maximal safe resection of gliomas near motor pathways in both asleep and awake interventions. Techniques used may include cortical mapping, subcortical stimulation, and monitoring motor and sensory evoked potentials (MEP and SSEP). These can reduce the rate of deficits without compromising the extent of resection.[18]

More recent innovations such as Laser in neurosurgery (LITT) or tumour treating fields (TTF) (as discussed below) are becoming increasingly available; their value and role in standard practice remain to be seen.

Post-operative care has made progress over the last two decades, with improved level of neuro-intensive care, early post-resection MRI and early holistic rehabilitation with the help of allied health professionals (physiotherapists, occupational and speech and language therapists) being the main contributing factors.

Radiotherapy and Chemotherapy

Radiotherapy can be used in the primary or adjuvant (following surgery) setting. It can be given alone, in combination with or sequentially to chemotherapy. Radiotherapy is typically given as daily fractions (#), the duration dependent on the tumour grade, and the age and fitness of the patient. A radiotherapy planning scan (CT/MRI) is the first step. At this juncture a thermoplastic shell, moulded to the patients' head, is created to facilitate reproducible patient positioning (Figure 3). The duration of each radiotherapy fraction is typically less than 10 minutes, during which time patients need to be able to lie still, on their own on a raised treatment couch (Figure 4).

CNS WHO Grade 2 Gliomas:

Following near or complete resection of a WHO grade 2 glioma, active surveillance with 6 to 12 monthly MRIs can be considered. Delaying adjuvant radiotherapy in this context does not have a negative impact on survival and can delay the toxicities associated with radiotherapy.[19] Patients with persistent neurological symptoms or patients who have had a subtotal resection (who are not being considered for further surgery) may benefit from immediate post operative radiotherapy.[20]

CNS WHO Grade 3 Gliomas:

Immediate post operative radiotherapy is indicated in most patients with a WHO grade 3 glioma, regardless of the degree of resection.

CNS WHO Grade 2 & Grade 3 Gliomas:

Radical radiotherapy schedules range from 50.4-59.4 Gray in 28-33#. 6 to 12 months of adjuvant chemotherapy with a combination of Procarbazine, Lomustine, Vincristine (PCV) or Temozolomide confers a PFS and OS benefit in both WHO grade 2 and 3 disease.[21,22,23] IDH mutant astrocytomas are less chemo-sensitive than oligodendrogliomas and so careful consideration of risk-benefit balance should be made in WHO grade 2 astrocytomas.[21]

Glioblastoma IDH-wildtype CNS WHO grade 4, & Astrocytoma IDH mutant CNS WHO grade 4:

Despite optimal therapy for these tumours, subsequent local recurrence is almost universally expected, associated with poor overall survival. The toxicities of treatment strategies therefore need to be carefully considered.

In patients under 70 years with a good performance status after surgery, treatment consists of radiotherapy over 6 weeks [60 Gray in 30#] with concurrent oral Temozolomide chemotherapy followed by 6 months of adjuvant Temozolomide [STUPP protocol]. [20] Since 2005, the Stupp protocol has been the standard treatment for high grade tumours, improving survival at 2 years post-treatment.[24] For those with MGMT promoter methylation, there is increased sensitivity to Temozolomide, and its use doubles 2-year overall survival compared to radiation alone.[24]

In patients over 70 years or in those with a poorer functional status a comprehensive frailty assessment should be used to guide treatment decisions. Hypofractionated radiotherapy can be considered; for example, 40 Gray in 15# over 3 weeks. This has a similar outcome in terms of survival compared to longer fractionation schedules to 60Gy. Single modality treatment is often better tolerated than combination treatment. Alternatively, Temozolomide can be given as the sole modality in MGMT methylated patients unfit for radiotherapy.[25, 26]

The need for supportive care, which may include steroids and anti-epileptics, should be addressed in all patients. Corticosteroids can be given before symptoms develop (prophylaxis) or after they develop, and are often beneficial for headaches, neurological symptoms or nausea and vomiting. It is important to remember to prescribe gastric protection alongside steroids, as well as to perform baseline and regular blood sugar monitoring to screen for steroid induced diabetes. Twice daily steroids should be taken morning and lunchtime to avoid insomnia. In up to 6% of adults, severe psychiatric reactions can occur with high doses of steroids. Tapering doses of steroids may be required for those who have required a prolonged course of treatment. Toxicity associated with

prolonged steroid use includes weight gain, diabetes, osteoporosis, Cushing's syndrome, and increased risk of infections.[27]

The frequency of seizure activity in patients with brain tumours ranges from 35-70%.[28] Seizures are managed with anti-epileptics, often in combination with corticosteroids if there is any suggestion of tumoral associated oedema. Anti-epileptics are started at the onset of seizures, as there is no evidence that starting them prophylactically in newly diagnosed brain tumours increases seizure free survival or reduces the frequency of first seizures at 6 months from diagnosis[28]. The choice of anti-epileptic is determined by both tumour type and patient factors. Levetiracetam is commonly utilised owing to its high efficacy, tolerability and lack of significant interactions with chemotherapy.[29] Doses are up titrated over weeks.

Glioblastoma patients in particular benefit from the early input of a palliative care team to help symptom management and avoid hospital admissions.

Best supportive care alone is usually the most suitable option in patients with poor functional status. Consideration should be given towards seizure control, management of delirium, impaired cognitive functioning and increased risk of falls, and psychological distress of both patients and carers.

COMPLICATIONS OF TREATMENT

Surgical complications & Management

Glioma surgery can be associated with a series of potential complications including the morbidity of the operation, bleeding (intra- or post-operatively), infection, wound healing complications (which may delay further oncological treatment), neurological deficits and seizures. The risk of infection and impaired wound healing may be exacerbated by steroids and adjuvant therapies. The risk of venous thromboembolism is also known to be increased in post-operative patients with malignant tumours. NICE guidance recommends that in addition to mechanical VTE prophylaxis pharmacological VTE prophylaxis is considered both pre and post operatively, stopping 24 hours pre surgery and continuing for 7 days post surgery, if the risk of VTE outweighs the risk of bleeding.[30] Surgery-related strokes are an important cause of morbidity following resection of gliomas. Stroke can impair patients' functional status, limiting further treatment options.[31] There is additionally a small risk to life with glioma surgery. Open and honest discussions with patients to counsel regarding risks, manage expectations and explain the balance of degree of resection versus functional preservation are imperative. A holistic approach and a multi-disciplinary team of allied health professionals and neuro-psychology support may help improve outcomes.

Radiotherapy complications and management:

Early side effects from radiotherapy accumulate during treatment and can peak up to two weeks after completion of treatment. Common short term side effects include fatigue, skin reactions, and hair loss in the treatment area. Less commonly patients can experience worsening intracerebral oedema causing headaches, nausea, vomiting and increased risk of seizures. Uncommonly, pre-existing neurological symptoms may worsen during treatment.

Long term side effects from radiotherapy are relevant in patients being treated for low-grade gliomas as these can be permanent and slowly worsen over years. These can include increased fatigue, impaired neurocognitive ability and increased risk of cerebrovascular disease. Rarer but significant risks include hypopituitarism, radio-necrosis and secondary radiation-induced malignancy.[24, 26]

Patients with acute side effect from radiotherapy or symptoms of raised ICP are treated with high dose corticosteroids, and seizures managed with anti-epileptics as discussed in the Radiotherapy and Chemotherapy section.

Chemotherapy complications and management:

Common toxicities from chemotherapy agents utilised for CNS tumours include fatigue, myelosuppression, increased risk of thromboembolism, nausea, and constipation. Patients require a pre-emptive anti-emetic regimen and may need laxative support. Prophylactic antibiotics may be prescribed to prevent Pneumocystis Jirovecii Pneumonia (PJP), but there is no consensus whether all patients should have antibiotics, the type of antibiotic or its duration.[32] Patients should be monitored for rashes, peripheral sensory neuropathy and derangement of liver biochemistry which may extend beyond cessation of treatment. Fertility preservations options should be sought prior to embarking on treatment.[1]

Monitoring and follow-up:

After treatment, patients are monitored clinically and radiologically. As progression may be clinically silent, dedicated surveillance imaging is recommended; table 2 summarises national guidance with frequency of imaging determined by tumour grade.[8] Response assessment can be challenging as contrast enhancement can be seen both as a sign of transformation or tumour progression, or as part of a treatment effect related to surgery or chemoradiotherapy (sometimes termed 'pseudoprogression'). Increasing T2/FLAIR signal abnormality can also be seen related to progression or to treatment, either via a small-vessel process or radiation-related demyelination. Advanced techniques such as perfusion, spectroscopy and DWI can help to differentiate between these entities and are captured by classification systems such as the Response Assessment in Neuro-Oncology

(RANO) criteria, which allows distinction between four categories based on treatment stage and MRI appearances: complete response, partial response, stable disease and progressive disease.[33]

Prognosis

Overarching prognostic factors thought to be associated with improved survival are younger age, good functional status, and greater extent of resection.[20] Median OS is impacted by tumour grade and the increasingly important molecular classification but also patient fitness for oncological management.

Survival estimates in the literature are wide-ranging, particularly in WHO Grade 2-3 gliomas. This is in part due to data collection prior to the addition of molecular testing into diagnostic criteria.

Grade 2 gliomas (combined pathology)	10.9[36] - 13.3 years [34]
Grade 3 IDH mutant 1p19q co-deleted oligodendroglioma	7.3 years – 14. 7 years [35]
Grade 3 IDH mutant astrocytoma	6.8 years [23]
Grade 4 glioblastoma, IDH-wildtype	Untreated: 2.3 months [37] Treated Unmethylated MGMT 15.3 months [38] Treated Methylated MGMT 21.7 months [38]
Grade 4 astrocytoma, IDH-mutant	Secondary progression from lower grade: 11.8m [39] Primary (de novo): 34.2m [39]

Management of recurrence

Even low-grade gliomas are incurable. Recurrent tumours may remain low-grade or may demonstrate transformation into higher grade tumours. Repeat biopsy or characteristic radiological appearances may guide prognostication and exclude treatment related changes.

Current clinical status (which often declines in the context of true progression), previous treatments received and the interval duration to recurrence determine management options. Patient preference and symptom burden is also key. Good performance status patients with a focal recurrence after a long surveillance period are likely to be the best candidates for further treatment. Salvage surgery, with the option of addition of Carmustine wafers to the resection cavity, chemotherapy (with temozolomide or PCV) and radiotherapy can all be considered either separately or in combination.[40] Recent trial data demonstrate significantly improved PFS and time to next intervention with the use of Vorasidenib, an IDH inhibitor, in patients with residual/recurrent IDH mutant Grade 2 gliomas after initial surgery (pending FDA approval).[41] Treatment options for

recurrent glioblastomas are suboptimal so enrolment onto clinical trials should be considered to facilitate access to emerging radiation techniques or therapies. Current trials are investigating the role of targeted agents, immunotherapy and stereotactic radiotherapy.

Future directions

Despite global efforts, the management of high-grade glioma hasn't changed significantly since the publication of the Stupp protocol in 2005.[24] Developments in whole-genome sequencing and epigenetic DNA-methylation screens have enabled improved molecular classification and prognostication; however, the low prevalence of known targetable mutations (*BRAF, NTRK, FGFR, EGFR, PIK3CA*) in adult tumours has meant this is yet to translate into meaningful clinical benefit.[42] Initiatives such as the Tessa Jowell BRAIN MATRIX platform trial are currently aiming to improve the speed and access to molecular diagnostics on a national scale, which will hopefully enable the future development and evaluation of novel biomarker-driven targeted agents.[43]

Following the success of novel immunotherapies in a variety of solid organ malignancies, there has also been recent investigation of their potential role in the management of glioma. The first and only positive trial was published in 2023, wherein the authors demonstrated that combination treatment with an autologous tumour lysate-loaded dendritic cell vaccine (*DCVax-L*) and temozolomide improved median overall survival from 16.5 months to 19.3 months when compared to SOC in patients with newly diagnosed glioblastoma.[44] However, due to concerns regarding trial design, there is ongoing debate as to whether this provides sufficient data to recommend *DCVax-L* in routine practice.[45] Unfortunately, all published trials investigating the use of concurrent, or adjuvant immune checkpoint inhibitors have yielded negative results.[46] Based upon promising translational data, ongoing active trials in the neo-adjuvant space are hoped to improve outcomes.[47] Other ongoing investigation includes the use of chimeric antigen receptor-T cell therapy or oncolytic immunovirotherapy. [48,49]

Finally, novel technologies such as tumour-treating fields (TTF or Optune®) have been developed, which administer alternating low- or intermediate-frequency electrical fields to the glioma through adhesive scalp electrodes. These are thought to exhibit anti-proliferative effects through a variety of molecular mechanisms, including impaired DNA-damage repair and promoting enhanced immunological responses.[50] Phase III trials have demonstrated that combination treatment with TTF + Standard of care (SOC) improved OS when compared to SOC alone in patients with newly diagnosed glioblastoma.[51] Furthermore, TTF demonstrated a similar OS with decreased toxicity,

when compared to physician-choice chemotherapy in patients with recurrent glioblastoma.[52] Whilst these data have led to FDA approval, TTF are not currently licensed by NICE.

Conclusion

Diffuse gliomas represent a spectrum of disease, ranging from a low-grade chronic condition with a prognosis measured in years, to a high-grade, devastating diagnosis with a prognosis of short months. Treatment is usually multimodal requiring surgery, radiotherapy and chemotherapy at various stages. Deciding on the optimal treatment schedule is a delicate balance of pathological, radiological and most importantly patient related factors. A named key worker, usually the oncology clinical nurse specialist, provides a vital role within this pathway. They are essential in providing patients and carers with information about symptom management and financial support, as well as directing patients towards members of the wider multidisciplinary team. All treatment options incur not inconsiderable side effects and access to physiotherapists, occupational therapists, speech and language therapists and neurocognitive therapists to help patients and carers navigate tumour and treatment related symptoms is essential.

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Figure Legends

Table 1. Recommended imaging protocol for diagnosis and surveillance of brain tumours, adapted from NICE guidelines.

Essential	T2	
	FLAIR* (±volumetric)	*Fluid attenuated inversion recovery
	DWI*	*Diffusion weighted imaging
	T1 pre contrast* volumetric	*Gadolinium based contrast agents
	T1 post contrast volumetric	
Optional	SWI*	*Susceptibility weighted imaging – useful for detecting haemorrhage/calcification
	Perfusion	Various techniques, most commonly using contrast
	Spectroscopy	Single or multivoxel techniques
	DTI*	*Diffusion tensor imaging; for surgical planning

Table 2. Recommended surveillance imaging protocol for brain tumours, adapted from NICE guidelines.

Grade of Tumour	Imaging Surveillance Schedule

All grades Post resection Post radiotherapy completion	Within 72 hours Within 3 months			
	0-2 years	2-4 years	5-10 years	>10 years
Grade 2 IDH mutated Grade 2/3 1p/19q co-deleted	3 months then every 6 months	Annually	Every 2 years	Every 1-2 years
Grade 2/3 IDH wild type Grade 3 1p/19q non-codeleted Grade 4	3 to 6 monthly	6 to 12 monthly* *in practice imaging for grade 4 tumours is often more frequent	Annually	Every 1-2 years

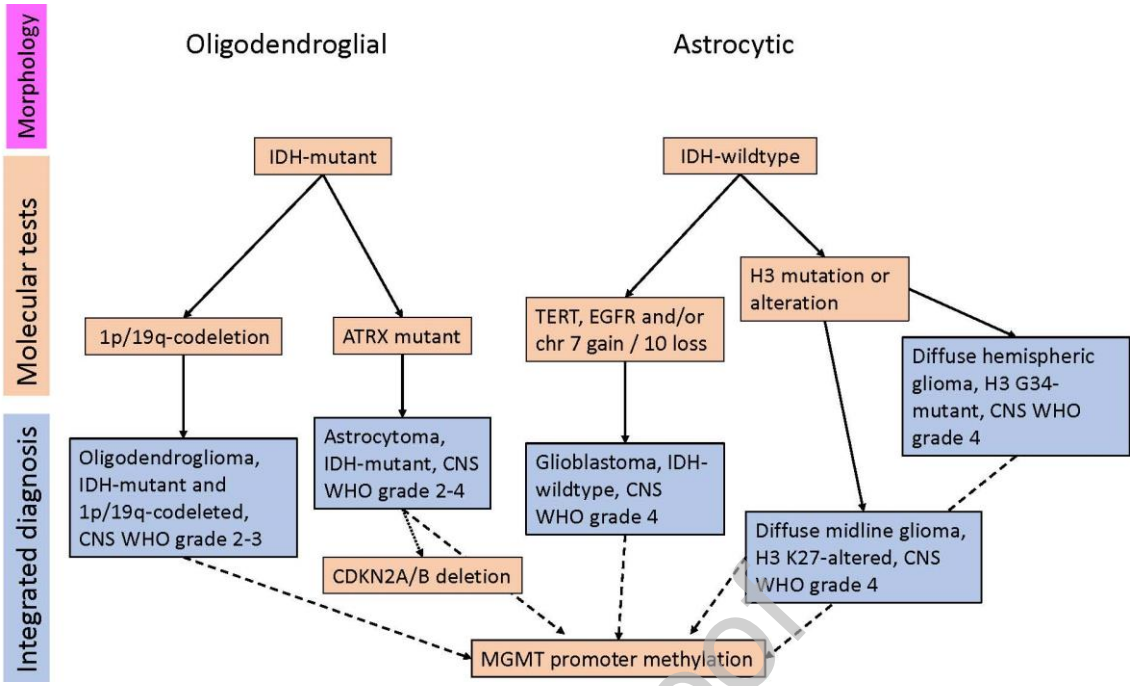

Figure 1. Schematic showing the diagnostic pathway used for diagnosis of diffuse gliomas in adults. Orange panels show molecular tests commonly used for diagnosis and prognosis: solid lines indicate diagnostic use; dotted lines indicate tests used in prognostication/grading; dashed lines indicate tests used for treatment response prediction. Blue panels indicate diagnostic entities as defined in the 2021 WHO Classification of Central Nervous System Tumours.

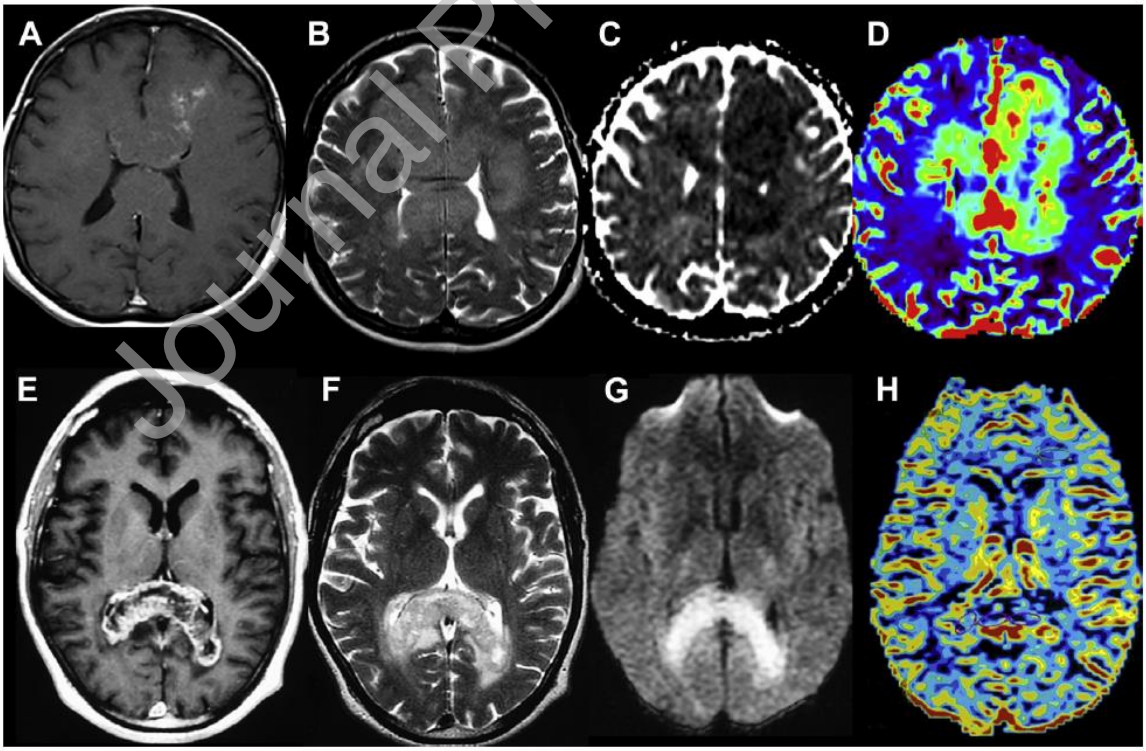

Fig. 2. Glioblastoma (*A–D*). A not enhancing (*A*, postcontrast FSE T1-weighted image), infiltrating lesion (*B*, T2-weighted image), with restricted diffusion (*C*, ADC map) and high perfusion on DSC-MR imaging map (*D*, rCBV map) is seen in the frontal lobes, which involves the corpus callosum. Lymphoma (*E–H*). A contrast-enhancing (*E*, postcontrast FSE T1-weighted image) heterogeneous lesion, surrounded by edema (*F*, T2-weighted image), with restricted diffusion (*G*, high *b* value DWI image) is seen in the splenium of the corpus callosum. In contrast to GBM, the lesion does not demonstrate high perfusion on DSC-MR imaging sequence (*H*, rCBV map).

Figure 2. Glioblastoma (A–D). A not enhancing (A, postcontrast FSE T1-weighted image), infiltrating lesion (B, T2-weighted image), with restricted diffusion (C, ADC map) and high perfusion on DSC-MR imaging map (D, rCBV map) is seen in the frontal lobes, which involves the corpus callosum. Lymphoma (E–H). A contrast-enhancing (E, postcontrast FSE T1-weighted image) heterogeneous lesion, surrounded by edema (F, T2-weighted image), with restricted diffusion (G, high b value DWI image) is seen in the splenium of the corpus callosum. In contrast to GBM, the lesion does not demonstrate high perfusion on DSC-MR imaging sequence (H, rCBV map).
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Figure 3. Image of a thermoplastic shell for immobilisation during radiotherapy.
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Figure 4. Image of a radiotherapy treatment machine: a linear accelerator. Image courtesy of The Brain Tumour Charity. All rights reserved.