NICE National Institute for Health and Care Excellence

NICE Pathways

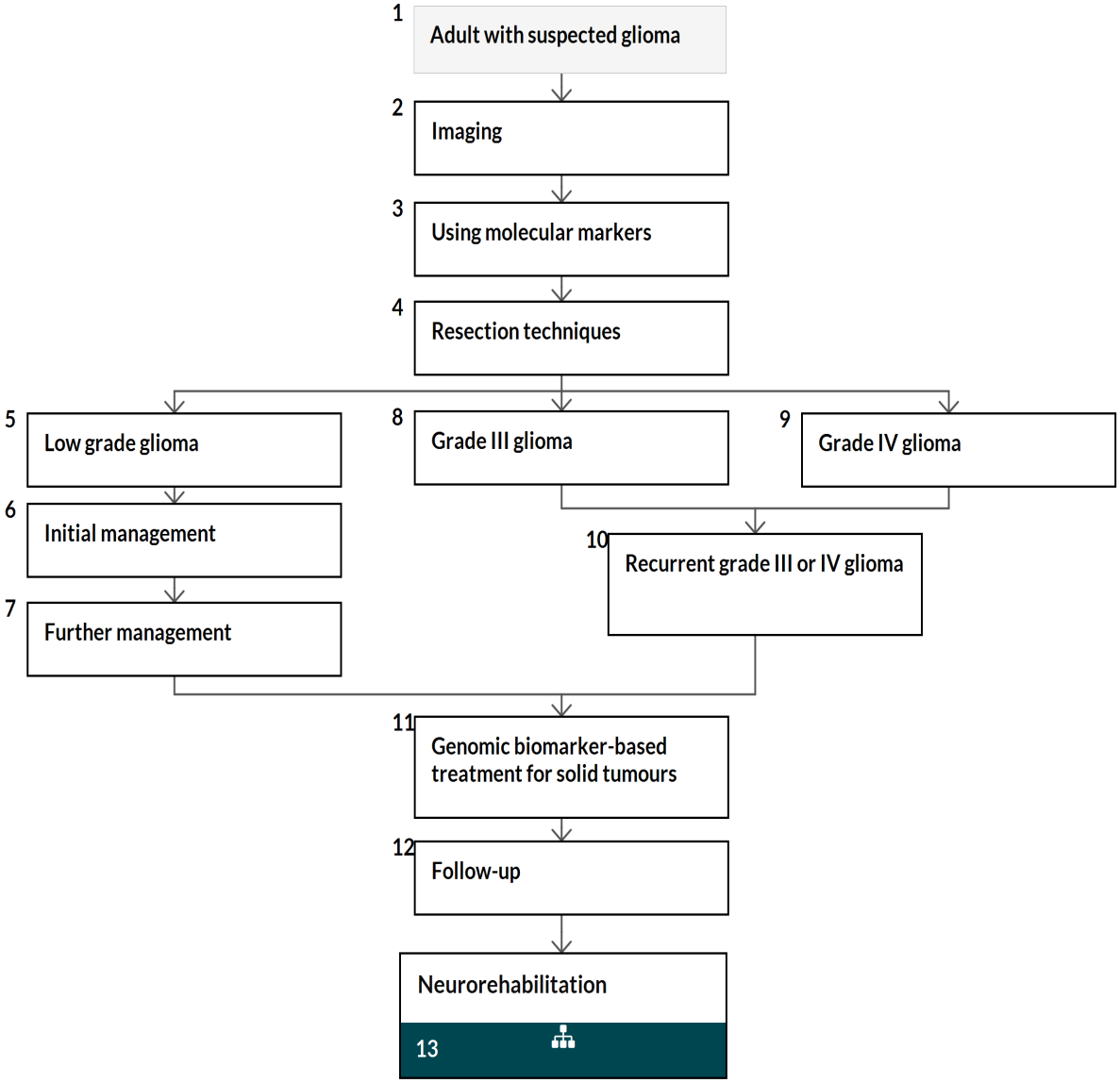
Brain cancer: glioma

NICE Pathways bring together everything NICE says on a topic in an interactive flowchart. NICE Pathways are interactive and designed to be used online.

They are updated regularly as new NICE guidance is published. To view the latest version of this NICE Pathway see:

http://pathways.nice.org.uk/pathways/brain-tumours-and-metastases
NICE Pathway last updated: 29 January 2021

This document contains a single flowchart and uses numbering to link the boxes to the associated recommendations.



1 Adult with suspected glioma

No additional information

2 Imaging

Offer standard structural MRI as the initial diagnostic test for suspected glioma, unless MRI is contraindicated.

Refer people with a suspected glioma to a specialist multidisciplinary team at first radiological diagnosis for management of their tumour.

Consider advanced MRI techniques, such as MR perfusion and MR spectroscopy, to assess the potential of a high-grade transformation in a tumour appearing to be low grade on standard structural MRI.

Why we made the recommendations

See information on imaging [See page 16].

3 Using molecular markers

Report all glioma specimens according to the latest version of the World Health Organisation classification. As well as histopathological assessment, include molecular markers such as:

- IDH1 and IDH2 mutations
- ATRX mutations to identify IDH mutant astrocytomas and glioblastomas
- 1p/19q codeletion to identify oligodendrogliomas
- histone H3.3 K27M mutations in midline gliomas
- BRAF fusion and gene mutation to identify pilocytic astrocytoma.

Test all high-grade glioma specimens for MGMT promoter methylation to inform prognosis and guide treatment.

Consider testing IDH-wildtype glioma specimens for TERT promoter mutations to inform prognosis.

Why we made the recommendations

See information on using molecular markers [See page 18].

4 Resection techniques

If a person has a radiologically-enhancing suspected high-grade glioma, and the multidiscliplinary team thinks that surgical resection of all enhancing tumour is possible, offer 5-aminolevulinic acid-guided resection as an adjunct to maximise resection at initial surgery.

Consider intraoperative MRI to help achieve surgical resection of both low-grade and high-grade glioma while preserving neurological function, unless MRI is contraindicated.

Consider intraoperative ultrasound to help achieve surgical resection of both low-grade and high-grade glioma.

Consider diffusion tensor imaging overlays in addition to standard neuronavigation techniques to minimise damage to functionally important fibre tracts during resection of both low-grade and high-grade glioma.

Consider awake craniotomy for people with low-grade or high-grade glioma to help preserve neurological function.

Discuss awake craniotomy and its potential benefits and risks with the person and their relatives and carers (as appropriate) so that they can make an informed choice about whether to have it. Only consider the procedure if the person is likely not to be significantly distressed by it.

Involve specialists as appropriate, such as neuropsychologists and speech and language therapists, before, during and after awake craniotomy.

Why we made the recommendations

See information on resection techniques [See page 20].

Photodynamic therapy

NICE has published interventional procedures guidance that photodynamic therapy for brain tumours should be used **only in the context of a formal research protocol**.

Preventing surgical site infections

See the NICE Pathway on preventing and treating surgical site infections.

5 Low grade glioma

The surgical expertise in the multidisciplinary team should include:

- access to awake craniotomy with language and other appropriate functional monitoring **and**
- expertise in intraoperative neurophysiological monitoring **and**
- access to neuroradiological support **and**
- access to intraoperative image guidance.

Why we made the recommendation

See information on initial management of low-grade glioma [See page 21].

6 Initial management

Consider surgical resection as part of initial management (within 6 months of radiological diagnosis) to:

- obtain a histological and molecular diagnosis, and
- remove as much of the tumour as safely possible after discussion of the possible extent of resection at multidisciplinary meeting and with the person with the brain tumour, and their relatives and carers.

If surgical resection is not appropriate, consider a biopsy to obtain a histological and molecular diagnosis.

Consider active monitoring without a histological diagnosis for lesions with radiological features typical of very low-grade tumours, for example, DNET or optic pathway glioma.

If people having active monitoring show radiological or clinical disease progression, discuss this at a multidisciplinary team meeting and consider:

- surgical resection **or**
- biopsy, if surgical resection is not possible.

Why we made the recommendations

See information on initial management of low-grade glioma [See page 21].

7 Further management

People with IDH mutated low-grade glioma

When delivering radiotherapy for people with IDH-mutated low-grade glioma, do not use a treatment dose of more than 54 Gy at 1.8 Gy per fraction.

After surgery, offer radiotherapy followed by up to 6 cycles of PCV chemotherapy for people who:

- have a 1p/19q codeleted, IDH-mutated low-grade glioma (oligodendroglioma) **and**
- are aged around 40 or over, or have residual tumour on postoperative MRI.

After surgery, consider radiotherapy followed by up to 6 cycles of PCV chemotherapy for people who:

- have a 1p/19q non-codeleted, IDH-mutated low-grade glioma (astrocytoma) **and**
- are aged around 40 or over, or have residual tumour on postoperative MRI.

Consider active monitoring for people who are aged around 40 or under with an IDH-mutated low-grade glioma and have no residual tumour on postoperative MRI.

Consider radiotherapy followed by up to 6 cycles of PCV chemotherapy for people with an IDH-mutated low-grade glioma who have not had radiotherapy before if they have:

- progressive disease on radiological follow-up **or**
- intractable seizures.

People with IDH-wildtype grade II glioma

Be aware that the prognosis for people with histologically confirmed IDH-wildtype grade II glioma may be similar to that of people with glioblastoma if other molecular features are consistent with glioblastoma. Take this into account when thinking about management options.

Why we made the recommendations

See information on further management of low-grade glioma [See page 22].

8 Grade III glioma

People with a Karnofsky performance status of 70 or more

After surgery, offer sequential radiotherapy and 4 to 6 cycles of PCV chemotherapy to people who have:

- a Karnofsky performance status of 70 or more, and
- a newly diagnosed grade III glioma with 1p/19q codeletion (anaplastic oligodendroglioma).

Agree with the person with anaplastic oligodendroglioma the order of PCV chemotherapy and radiotherapy after discussing the potential advantages and disadvantages of each option with them (see factors to take into account when deciding whether to have PCV or radiotherapy first for management of anaplastic oligodendroglioma [See page 16]).

After surgery, offer radiotherapy followed by up to 12 cycles of adjuvant temozolomide to people who have:

- Karnofsky performance status of 70 or more and
- a newly diagnosed IDH-wildtype or mutated grade III glioma without 1p/19q codeletion (anaplastic astrocytoma).

For guidance on using temozolomide for treating newly diagnosed grade III glioma, see below.

See why we made the recommendations on managing grade III glioma in people with a Karnofsky performance status of 70 or more following surgery [See page 23].

Temozolomide and carmustine for people with high grade glioma

The following recommendations are from NICE technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

Temozolomide and carmustine implants have been appraised separately for the treatment of newly diagnosed high-grade glioma. On the basis of the evidence presented to the Committee, no recommendation can be made regarding the sequential use of these treatments for newly diagnosed high-grade glioma.

Temozolomide

Temozolomide, within its licensed indications, is recommended as an option for the treatment of

newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1.

Carmustine implants

Carmustine implants, within their licensed indications, are recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.

Treatment with carmustine implants should be provided only within specialist centres that in general conform to guidance in 'Improving outcomes for people with brain and other central nervous system tumours' (NICE cancer service guidance 2006), and should be supervised by specialist neurosurgeons who spend at least 50% of their clinical programmed activities in neuro-oncological surgery. The specialists should also have access to:

- multidisciplinary teams to enable preoperative identification of patients in whom maximal resection is likely to be achievable
- magnetic resonance imaging (MRI) to enable preoperative identification of patients in whom maximal resection is likely to be possible, and
- image-directed technology, such as neuronavigation, for use intraoperatively to assist the achievement of maximal resection.

Carmustine implants are not recommended for the treatment of newly diagnosed high-grade glioma for patients in whom less than 90% of the tumour has been resected.

NICE has written information for the public on carmustine and temozolomide.

Treatments not to offer or that evidence does not support

Do not offer nitrosoureas (for example, CCNU [lomustine]) concurrently with radiotherapy to people with newly diagnosed grade III glioma.

If asked, advise people with an initial diagnosis of grade III glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of:

- cannabis oil
- immunotherapy
- ketogenic diets
- metformin
- statins

- valganciclovir.

See why we made the recommendations on treatments not to offer or that evidence does not support for grade III glioma [See page 23].

9 Grade IV glioma

People with a Karnofsky performance status of 70 or more

Offer radiotherapy using 60 Gy in 30 fractions with concomitant temozolomide followed by up to 6 cycles of adjuvant temozolomide, for people aged around 70 or under who have:

- a Karnofsky performance status of 70 or more **and**
- had maximal safe resection, or biopsy when resection is not possible, for a newly diagnosed grade IV glioma (glioblastoma).

Offer radiotherapy using 40 Gy in 15 fractions with concomitant and up to 12 cycles of adjuvant temozolomide for people aged around 70 or over who have:

- a Karnofsky performance status of 70 or more **and**
- a newly diagnosed grade IV glioma (glioblastoma) with MGMT methylation.

Consider radiotherapy using 40 Gy in 15 fractions with concomitant and up to 12 cycles of adjuvant temozolomide for people aged around 70 or over who have:

- a Karnofsky performance status of 70 or more **and**
- a newly diagnosed grade IV glioma (glioblastoma) without MGMT methylation or for which methylation status is unavailable.

For guidance on using temozolomide for treating newly diagnosed grade IV glioma (glioblastoma), see below.

See why we made the recommendations on managing grade IV glioma [See page 24].

Temozolomide and carmustine for people with high grade glioma

The following recommendations are from NICE technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

Temozolomide and carmustine implants have been appraised separately for the treatment of newly diagnosed high-grade glioma. On the basis of the evidence presented to the Committee,

no recommendation can be made regarding the sequential use of these treatments for newly diagnosed high-grade glioma.

Temozolomide

Temozolomide, within its licensed indications, is recommended as an option for the treatment of newly diagnosed glioblastoma multiforme (GBM) in patients with a World Health Organization (WHO) performance status of 0 or 1.

Carmustine implants

Carmustine implants, within their licensed indications, are recommended as an option for the treatment of newly diagnosed high-grade glioma only for patients in whom 90% or more of the tumour has been resected.

Treatment with carmustine implants should be provided only within specialist centres that in general conform to guidance in 'Improving outcomes for people with brain and other central nervous system tumours' (NICE cancer service guidance 2006), and should be supervised by specialist neurosurgeons who spend at least 50% of their clinical programmed activities in neuro-oncological surgery. The specialists should also have access to:

- multidisciplinary teams to enable preoperative identification of patients in whom maximal resection is likely to be achievable
- magnetic resonance imaging (MRI) to enable preoperative identification of patients in whom maximal resection is likely to be possible, and
- image-directed technology, such as neuronavigation, for use intraoperatively to assist the achievement of maximal resection.

Carmustine implants are not recommended for the treatment of newly diagnosed high-grade glioma for patients in whom less than 90% of the tumour has been resected.

NICE has written information for the public on carmustine and temozolomide.

People aged 70 or over with Karnofsky performance status of less than 70

Consider best supportive care alone for people aged around 70 or over who have:

- a grade IV glioma (glioblastoma) **and**
- a Karnofsky performance status of under 70.

See why we made the recommendations on managing grade IV glioma [See page 24].

Other people

For people with an initial diagnosis of grade IV glioma (glioblastoma) not covered in the above recommendations, consider the treatment options of:

- radiotherapy using 60 Gy in 30 fractions with concurrent and up to 6 cycles of adjuvant temozolomide
- radiotherapy alone using 60 Gy in 30 fractions
- hypofractionated radiotherapy
- up to 6 cycles of temozolomide alone if the tumour has MGMT methylation and the person is aged around 70 or over
- best supportive care alone.

See why we made the recommendations on managing grade IV glioma [See page 24].

Reviewing treatment options

Assess the person's performance status throughout the postoperative period and review treatment options for grade IV glioma (glioblastoma) if their performance status changes.

See why we made the recommendations on managing grade IV glioma [See page 24].

Treatments not to offer or that evidence does not support

Do not offer bevacizumab as part of management of a newly diagnosed grade IV glioma (glioblastoma).

Do not offer tumour-treating fields as part of management of a newly diagnosed grade IV glioma (glioblastoma).

If asked, advise people with an initial diagnosis of grade IV glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of:

- cannabis oil
- immunotherapy
- ketogenic diets
- metformin
- statins
- valgancyclovir.

See why we made the recommendations on treatments not to offer or that evidence does not support for grade IV glioma [See page 25].

NICE has produced a visual summary on grade IV glioma.

10 Recurrent grade III or IV glioma

When deciding on treatment options for people with recurrent high-grade glioma, take into account:

- Karnofsky performance status
- the person's preferences
- time from last treatment
- tumour molecular markers
- what their last treatment was.

Consider PCV or single agent CCNU (lomustine) as an alternative to temozolomide for people with recurrent high-grade glioma.

For guidance on using temozolomide as an option for treating recurrent high-grade glioma, see below.

Consider best supportive care alone for high-grade glioma if other treatments are not likely to be of benefit, or if the person would prefer this. Refer to the NICE guideline on improving supportive and palliative care for adults with cancer.

See also NICE's recommendations on caring for an adult at the end of life.

For people with focally recurrent high-grade glioma, the multidisciplinary team should also consider the treatment options of:

- further surgery
- further radiotherapy.

See why we made the recommendations on managing recurrent grade III or IV glioma [See page 25].

Temozolomide

The following recommendations are from NICE technology appraisal guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer)

Temozolomide is recommended as an option for treating malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy only if the person has a Karnofsky performance status score greater than or equal to 70 and a life expectancy of 12 weeks or more.

When using the Karnofsky performance status score, clinicians should be aware of the need to secure equality of access to treatment for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to their prognosis for malignant glioma. For such people clinicians should make appropriate judgements about performance status, taking into account the person's usual functional capacity and need for assistance with activities of daily living.

People whose treatment with temozolomide is not recommended in this NICE guidance, but was started within the NHS before this guidance was published, should be able to continue treatment until they and their NHS clinician consider it appropriate to stop.

NICE has written information for the public on temozolomide.

Treatment not to offer or that evidence does not support

Do not offer bevacizumab, erlotinib, or cediranib, either alone or in combination with chemotherapy, as part of management of a recurrent high-grade glioma.

Do not offer tumour treating fields (TTF) as part of management of a recurrent high-grade glioma.

If asked, advise people who have a recurrent high-grade glioma (and their relatives and carers, as appropriate) that the available evidence does not support the use of:

- cannabis oil
- immunotherapy
- ketogenic diets
- metformin
- statins
- valgancyclovir.

See why we made the recommendations on treatments not to offer or that evidence does not support for recurrent high-grade glioma [See page 26].

Carmustine implants for recurrent glioblastoma multiforme

The NICE technology appraisal of carmustine implants for the treatment of recurrent glioblastoma multiforme was terminated because no evidence submission was received from the manufacturer or sponsor of the technology. Therefore NICE was unable to make a recommendation about the use of this technology in the NHS.

11 Genomic biomarker-based treatment for solid tumours

The point at which to use genomic biomarker-based therapy in solid tumour treatment pathways is uncertain. See the NICE Pathway on genomic biomarker-based treatment for solid tumours for guidance on specific treatments.

12 Follow-up

Clinical reviews

Offer regular clinical review for people with glioma to assess changes in their physical, psychological and cognitive wellbeing.

Base decisions on the timing of regular clinical reviews and follow-up imaging for people with glioma on:

- any residual tumour
- life expectancy
- the person's preferences (see factors to take into account when deciding on frequency of follow-up for people with glioma [See page 17])
- treatments used before
- treatment options available
- tumour subtype.

Consider using the follow-up schedule given in the possible regular clinical review schedule for people with glioma depending on grade of tumour [See page 18].

For people with glioma having routine imaging:

- explain to them, and their relatives and carers, that imaging can be difficult to interpret and results can be of uncertain significance **and**
- be aware that having routine imaging and waiting for the results may cause anxiety.

Arrange a clinical review, including appropriate imaging, for people with glioma who develop new or changing neurological symptoms or signs at any time.

Baseline follow-up MRI

Consider a baseline MRI scan within 72 hours of surgical resection for all types of glioma.

Consider a baseline MRI scan 3 months after the completion of radiotherapy for all types of glioma.

Using MRI scans

Consider standard structural MRI as part of regular clinical review for people with glioma, to assess for progression or recurrence, unless MRI is contraindicated.

Consider advanced MRI techniques, such as MR perfusion, diffusion tensor imaging and MR spectroscopy, if findings from standard imaging are unclear about whether there is recurrence and early identification is potentially clinically helpful.

Why we made the recommendations

See information on glioma follow-up [See page 26].

13 Neurorehabilitation

See Brain tumours and metastases / Brain tumours and metastases overview / Neurorehabilitation

Factors to take into account when deciding whether to have PCV or radiotherapy first for management of anaplastic oligodendroglioma

	PCV **first**	**Radiotherapy first**
Overall survival	No clinically important difference.	No clinically important difference.
Progression-free survival	No clinically important difference.	No clinically important difference.
Fertility preservation	Trying to preserve fertility may cause a delay in the start of treatment.	Allows additional time for fertility preservation without delaying treatment.
Planning treatment around important life events	Initially much less contact with the health system, but potentially more fatigue. Harder to give a precise date for when radiotherapy will start, as people's reaction to chemotherapy is less predictable.	Initially much more contact with the health system: daily visits to radiotherapy department lasting several weeks. Timing of start of chemotherapy much more predictable.

Imaging

The evidence indicated that standard structural MRI is useful in distinguishing high-grade from low-grade glioma. The committee noted that this knowledge will inform management. Based on their experience, the committee recommended a protocol that they defined as a minimum standard for imaging acquisition.

No evidence was found on more advanced MRI techniques. However, the committee agreed that in their experience such techniques can be useful for assessing malignant features of a tumour – in particular, for ensuring that high-grade tumours are not misdiagnosed as low-grade tumours, which could have serious consequences for people who receive suboptimal

management as a result. However the committee explained that a specialist multidisciplinary team would be needed to interpret features of the scan and decide management, even if advanced techniques were used.

How the recommendations might affect practice

Currently, various imaging strategies are used in different centres and depending on the person's circumstances. These recommendations aim to reduce variation in practice, and ensure that images obtained at different sites and using different equipment can be more accurately compared. Some centres may need to change their imaging protocols. This might increase or reduce costs depending on the imaging protocols which are currently in place.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Factors to take into account when deciding on frequency of follow-up for people with glioma

Possible advantages of more frequent follow-up	Possible disadvantages of more frequent follow-up
May identify recurrent disease earlier which may increase treatment options or enable treatment before people become symptomatic.	There is no definitive evidence that identifying recurrent disease early improves outcomes.
May help provide information about the course of the illness and prognosis.	May increase anxiety if changes of uncertain significance are detected on imaging.
Some people can find more frequent imaging and hospital contact reassuring. Provides an opportunity to identify patient or carer needs (such as psychosocial support and late side effects of treatment).	Some people can find more frequent imaging and hospital contact burdensome and disruptive – they feel their life revolves around their latest scan. There may be a financial cost from taking time

	off work and travelling to appointments.
	More imaging and follow-up is resource intensive for the NHS.

Using molecular markers

Molecular markers are an emerging and important area in the treatment of brain tumours. The committee looked for evidence on these markers but did not find any. However, they noted that there are some molecular markers for which the evidence of benefit if tested is overwhelming, as reported in studies identified in searches for other review questions. This applies in particular for MGMT promoter methylation and TERT promoter mutations in IDH-wildtype glioma, although the committee agreed the evidence was of a higher quality in the first case than the second. The committee agreed that even these markers are not being consistently tested for and that testing should be standardised. Therefore they made recommendations based on their knowledge and experience, highlighting the WHO classification, to ensure that all centres follow a consistent process for assessing and interpreting information on molecular markers. This was important, since failure to consistently report molecular markers can mislead clinicians or limit treatment options.

How the recommendations might affect practice

As testing for molecular markers is relatively new, practice can vary widely and this is to be expected. In principle there should not be a major change, although the time taken to implement the new molecular tests will vary significantly between centres.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Possible regular clinical review schedule for people with glioma depending on grade of tumour

	Years after end of treatment:

<table>
<tr><th></th><th>0 to 1</th><th>1 to 2</th><th>2 to 3</th><th>3 to 4</th><th>[5 to 10}</th><th>>10 (for the rest of life)</th></tr>
<tr><td>Grade I</td><td colspan="6">Scan at 12 months, then:
consider discharge if no tumour visible on imaging unless completely resected pilocytic astrocytoma
consider ongoing imaging at increasing intervals for 15 years for completely resected pilocytic astrocytoma
consider if ongoing imaging is needed at a rate of once every 1 to 3 years for the rest of the person's life if the tumour is visible on imaging</td></tr>
<tr><td>Grade II 1p/19q non-codeleted, IDH mutated</td><td colspan="2" rowspan="3">Scan at 3 months, then every 6 months</td><td rowspan="3">Annually</td><td rowspan="3">Every 1 to 2 years</td><td colspan="2" rowspan="3">Consider ongoing imaging every 1 to 2 years</td></tr>
<tr><td>Grade II 1p/19q codeleted</td></tr>
<tr><td>Grade III 1p/19q codeleted</td></tr>
<tr><td>Grade II IDH-wildtype</td><td colspan="2" rowspan="3">Every 3 to 6 months</td><td rowspan="3">Every 6 to 12 months</td><td rowspan="3">Annually</td><td colspan="2" rowspan="3">Consider ongoing imaging every 1 to 2 years</td></tr>
<tr><td>Grade III 1p/19q non-codeleted</td></tr>
<tr><td>Grade IV (Glioblastoma)</td></tr>
</table>

Resection techniques

There was evidence that 5-ALA, intraoperative MRI and diffusion tensor imaging could improve either the extent or safety of resection (particularly the preservation of neurological function). The committee noted that a combination of techniques might be needed to optimise both the extent and safety of resection for a particular surgical plan. The committee concluded that the evidence for MRI could be generalised to intraoperative ultrasound on the basis of their clinical experience, and therefore that clinicians should be able to choose either technique depending on availability.

The evidence for awake craniotomy was equivocal (non-significant differences compared with surgery under general anaesthesia), therefore from the evidence it was not possible to conclude that awake craniotomy would benefit all people with glioma. This is in line with the committee's clinical experience that some people benefit from the procedure (in terms of preserving language, motor and visual function) but others are harmed – particularly from psychological effects, which act as a contraindication to awake craniotomy. The committee described how better preoperative procedures could reduce the number of people distressed by the procedure.

How the recommendations might affect practice

Some techniques recommended by the committee require a very high level of intraoperative skill, and this might have resource implications for hospitals recruiting people with these specialist skills. There is significant variation in the current provision of psychological support for people before and during awake craniotomy, and implementing this could carry a high cost to an individual unit.

If a unit does not have access to intraoperative ultrasound or MRI, the cost of acquiring this equipment could be substantial (MRI is relatively expensive, ultrasound is relatively cheap). However the committee concluded that most units should have access to one or the other already. Therefore the only resource impact would be if a unit currently using intraoperative ultrasound decided that the additional evidence for preservation of neurological function in intraoperative MRI justified the cost of switching machines. However, the committee thought this was unlikely to happen.

Using 5-ALA is associated with a high cost, and 5-ALA-guided surgery needs a non-standard fluorescence-detecting microscope. Therefore the resource impact of this recommendation is likely to be high in all settings, and very high in settings without access to a fluorescence-detecting microscope. The anticipated resource impact of this recommendation is greater than

£1 million per year.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Initial management of low-grade glioma

There was evidence that optimal resection of a large percentage of the tumour improved survival for people with low-grade glioma. The committee noted that it is sometimes not appropriate to offer maximal safe resection (for example, if the balance of risks and benefits favours not resecting all areas) and that a specialist surgical team should look at the value of doing an operation given its safe extent. They agreed that biopsy should be considered in these cases, based on limited evidence showing improved overall survival after biopsy compared with active monitoring. However, the committee also concluded that some tumours were of such limited risk that the risks of surgery outweighed the possible gain of biopsy or resection.

The committee described how there was no evidence for immediate intervention, but that intervention should not be delayed due to the probability that surgical resection would have benefit for the person with the tumour. They therefore recommended intervention within 6 months, to allow for time to discuss treatment options with the person with the tumour. This also to allows for the possibility of a second imaging sequence to be done later to look for progression and to assess for symptom change, as the committee also recognised that a proportion of low-grade gliomas have unfavourable gene profiles (for example, IDH wild-type) that make them more like high-grade tumours from a prognostic perspective.

A small number of people might have had initial treatment before it was standard practice to save a tissue sample for biopsy, and these people would currently be actively monitored. Based on their experience the committee agreed that these people may not need further surgery as long as their condition is stable (that is, they are not showing radiological or clinical disease progression).

How the recommendations might affect practice

The recommendations are likely to change practice at some centres, and remove unnecessary variation. There are currently differences between centres in which molecular diagnoses are performed and in treatment of very low-risk low-grade tumours. This is partly because low-grade gliomas may be managed by non-expert surgical teams.

The recommendation about the management of low-grade gliomas that have been managed but then progress is unlikely to substantially change practice, as management would be largely unchanged.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Further management of low-grade glioma

There was evidence that PCV chemotherapy after radiotherapy improved overall survival and progression-free survival compared with radiotherapy alone. The committee discussed how the evidence for the exact regime was complex, and used their judgement to recommend possible sequence and dose. In addition, the committee noted that there are some circumstances where radiotherapy and PCV might not be appropriate (particularly for the very lowest-concern and highest-concern low-grade tumours) and made recommendations based on their experience in these cases.

The committee included approximate age cut-offs based on evidence showing that treatment improved survival in people aged around 40 or over with or without residual tumour, and their clinical judgement that treatment would be unlikely to be of benefit for people aged around 40 or under without residual tumour.

The committee found no evidence on the treatment of IDH-wildtype grade II glioma. They determined that management of this type of glioma was likely to be different from other low-grade glioma, as IDH-wildtype grade II glioma behaves more like a high-grade glioma. The committee therefore made a research recommendation on whether treating this tumour type more like a grade II glioma or grade IV glioma was most beneficial.

How the recommendations might affect practice

These recommendations aim to standardise practice. They will probably result in the same amounts of chemotherapy and radiotherapy being given, but these treatments will be more precisely targeted and it is possible that they will be given earlier. This would result in more people requiring long-term treatment for the side effects of radiation and chemotherapy. More people are likely to have active monitoring alone, which is not likely to create a resource impact.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Managing grade III glioma in people with a Karnofsky performance status of 70 or more following surgery

The committee considered evidence for grade III and grade IV glioma separately.

Based on randomised control trial evidence, the committee recommended radiotherapy and either PCV or temozolomide chemotherapy, depending on tumour subtype and performance status, for people with grade III glioma.

How the recommendations might affect practice

Adjuvant PCV for treating codeleted grade III glioma is standard practice, but adjuvant temozolomide for non-codeleted grade III gliomas is a change in practice. However, some centres may already have started to adopt this as standard care, since the results of the study supporting this treatment were made publicly available in 2016.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Treatments not to offer or that evidence does not support for grade III glioma

The committee considered evidence for grade III and grade IV glioma separately.

Based on the available evidence, the committee recommended that some treatments should not be offered because they were harmful. They also agreed, based on their experience, that it would be useful for healthcare professionals to tell people with glioma that no evidence had been found to indicate that certain treatments are beneficial.

How the recommendations might affect practice

Adjuvant PCV for treating codeleted grade III glioma is standard practice, but adjuvant temozolomide for non-codeleted grade III gliomas is a change in practice. However, some centres may already have started to adopt this as standard care, since the results of the study supporting this treatment were made publicly available in 2016.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Managing grade IV glioma

The committee considered evidence for grade III and grade IV glioma separately.

The committee saw some evidence demonstrating improved overall survival in some groups of people with grade IV glioma who had radiotherapy with concurrent and adjuvant temozolomide (compared with radiotherapy alone). However, based on their clinical experience they were unsure that these results could be generalised to all people with grade IV glioma, so suggested a range of possible treatments that can be considered for other groups, depending on the exact clinical characteristics of the tumour.

Approximate age cut-offs for people with grade IV glioma were specified by the committee based on evidence that a radiotherapy dose of 40 Gy did not result in lower survival in people aged around 70 or over compared with a 60 Gy dose. Therefore a lower radiotherapy dose is likely to cause fewer side effects without compromising clinical effectiveness for this group.

The committee were aware that the prognosis of people with a grade IV glioma and a low performance status was poor, and recommended palliative care be considered. However the committee did not find any evidence on whether earlier or later palliative care was most beneficial for people who might need it. They therefore made a research recommendation on this topic, with the aim of finding out the point in the treatment pathway when it would be most beneficial for people with this type of glioma to have palliative care.

How the recommendations might affect practice

For younger people with a grade IV glioma and a good performance status, a course of radiotherapy with concurrent and adjuvant temozolomide is standard care. However, for people aged around 70 and over, particularly those with a glioma with methylated MGMT, the use of concurrent and adjuvant temozolomide with 15 fractions of radiotherapy is a change of practice that will probably result in more people being treated. This is a relatively small group of people, and so the recommendation is unlikely to have a significant resource impact.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Treatments not to offer or that evidence does not support for grade IV glioma

Based on the available evidence, the committee recommended that certain treatments should not be offered. This included tumour treating fields (TTF) based on published health economic evidence that they are not an efficient use of NHS resources. They also agreed, based on their clinical experience, that it would be useful for healthcare professionals to tell people with glioma that no evidence had been found to suggest that certain treatments are beneficial.

How the recommendations might affect practice

For younger people with a grade IV glioma and a good performance status, a course of radiotherapy with concurrent and adjuvant temozolomide is standard care. However, for people aged around 70 and over, particularly those with a glioma with methylated MGMT, the use of concurrent and adjuvant temozolomide with 15 fractions of radiotherapy is a change of practice that will probably result in more people being treated. This is a relatively small group of people, and so the recommendation is unlikely to have a significant resource impact.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Managing recurrent grade III or IV glioma

Based on the available evidence, the committee recommended that treatment options for people with recurrent glioma should include temozolomide, PCV and single-agent CCNU (lomustine). No evidence was found to indicate which of these 3 options is likely to lead to the best outcomes, and on the basis of their clinical experience the committee concluded that the choice of treatment should take several factors into account, including the individual features of the tumour and the preferences of the person. The committee also highlighted the possibility of considering supportive care alone.

How the recommendations might affect practice

These recommendations reflect standard treatment for recurrent high-grade glioma, and therefore should not represent a substantial change in practice.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Treatments not to offer or that evidence does not support for recurrent grade III or IV glioma

Based on the available evidence, the committee recommended that certain treatments should not be offered. This included tumour treating fields (TTF) on the basis of evidence of some clinical benefit but indirect published health economic evidence, in people with newly diagnosed high-grade glioma, that they are not cost-effective. They also agreed, based on their clinical experience, that it would be useful for healthcare professionals to tell people with glioma that no evidence had been found to suggest that certain treatments are beneficial.

How the recommendations might affect practice

These recommendations reflect standard treatment for recurrent high-grade glioma, and therefore should not represent a substantial change in practice.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Glioma follow-up

In the absence of evidence, the committee made recommendations based on their clinical experience. They recommended regular clinical review as the only plausible way of identifying and potentially managing recurrence or changing symptoms. They also recommended the review schedule take into account all of the person's relevant characteristics, including grade of tumour. As this is quite difficult to work out, the committee suggested a schedule of clinical reviews that is likely to be beneficial for a 'typical' person, which can be amended as needed to take into account individual variation. The committee did not uncover evidence on who should do the follow-up and so did not make a recommendation on this topic as it would vary according to clinical need, but discussed how it could be – for example – the local oncologist, neuro-oncologist, neurologist, neurosurgeon, clinical nurse specialist, or GP.

As regular clinical review should include imaging, based on their experience the committee suggested an MRI sequence which they believed would be suitable to monitor for recurrence. They discussed how advanced MRI techniques might be valuable, but as these techniques are time-consuming and difficult to interpret the committee concluded they should only be recommended under certain circumstances where extra information was likely to substantially alter treatment plans. The committee recommended that any change in neurological signs or symptoms (which would include changes in behavioural, emotional and psychological signs and

symptoms) be treated as a sign of a potential change to the tumour, and therefore recommended clinical review outside the usual schedule in order to investigate this.

The committee believed that a dedicated supportive care clinic could improve outcomes for people with low-grade glioma, but did not find any evidence on this. Therefore they made a research recommendation on improving the long-term outcomes of people with low-grade glioma.

How the recommendations might affect practice

The recommendations are in line with current best practice, and should standardise practice. They are unlikely to cause a significant increase in resource use, but there may be some additional costs or changes in service configuration if practice differs in a particular centre.

The imaging sequences are recommended on the basis of evidence for the appropriate sequences for initial diagnosis, and so might not be the standard sequence for follow-up in all centres. As a result, adopting the recommended sequences might create some additional workload for some centres. However the recommendations for exact schedules are examples based on consensus in the committee, and there is therefore flexibility for centres to adapt these to their own models, limiting resource impact.

For more information, see evidence review A: investigation, management and follow-up of glioma.

Glossary

active monitoring

(regular clinical and radiological review of a person with a brain tumour or brain metastases who are not currently having treatment for their cancer)

DNET

dysembryoplastic neuroepithelial tumour

Regular clinical review

(outpatient review of the person with a brain tumour or brain metastases at a planned interval from the previous visit in order to assess symptoms and care needs, to provide support and

treatment and to perform imaging when appropriate)

PCV

(procarbazine, CCNU (lomustine) and vincristine)

standard structural MRI

(defined as T2 weighted, FLAIR, DWI series and T1 pre- and post-contrast volume)

Sources

Brain tumours (primary) and brain metastases in adults (2018 updated 2021) NICE guideline NG99

Carmustine implants for the treatment of recurrent glioblastoma multiforme (terminated appraisal) (2008) NICE technology appraisal 149

Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (2007) NICE technology appraisal guidance 121

Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (2001 updated 2016) NICE technology appraisal guidance 23

Your responsibility

Guidelines

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

Local commissioners and providers of healthcare have a responsibility to enable the guideline

to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Technology appraisals

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take these recommendations fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this interactive flowchart is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the recommendations to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Medical technologies guidance, diagnostics guidance and interventional procedures guidance

The recommendations in this interactive flowchart represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare

professionals are expected to take these recommendations fully into account. However, the interactive flowchart does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Commissioners and/or providers have a responsibility to implement the recommendations, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this interactive flowchart should be interpreted in a way that would be inconsistent with compliance with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.