Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer)

Technology appraisal guidance
Published: 26 April 2001
Last updated: 3 March 2016

www.nice.org.uk/guidance/ta23
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance 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.
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1 Guidance

1.1 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.

1.2 This recommendation has been updated by recommendation 1.1 in the NICE technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

1.3 This recommendation has been updated by recommendation 1.1 in the NICE technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.

1.4 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.
2 Clinical Need and Practice

2.1 Although brain tumours account for only 1.5% of all primary cancers and 2% of cancer deaths, they result in 7% of life-years lost before the age of 70. About 55% of primary brain cancers occur in males. Approximately 29% of adult patients survive one year after diagnosis and 13% survive 5 years.

2.2 Malignant glioma is the most common form of primary brain tumour. The incidence in England and Wales is 4 per 100,000 population. There are about 3,500 new cases in the UK each year. They represent 50% to 60% of all primary brain tumours, and about 0.8% of all malignant neoplasms in adults in England and Wales.

2.3 Anaplastic, or grade III, astrocytomas (AA) comprise some 30–35% of malignant gliomas, glioblastoma multiforme (GBM), also known as grade IV astrocytomas, 40–45% and anaplastic, or grade III, oligodendrogliomas (AO) 5–15%. The average age of people with GBM is 10 years greater than that of people with AA. Median survival time from diagnosis for GBM is of the order of 5 to 12 months, but for AA is longer at 11 to 36 months. The WHO grading system for gliomas ranges from I (benign) to IV (malignant and aggressive) and is detailed in appendix E.

2.4 People with malignant glioma can suffer from a range of symptoms and impairments. Some symptoms may be general and others may be specific to the area of brain where the tumour is located. General symptoms include headache, anorexia, nausea, vomiting, seizures, drowsiness, personality changes, and cognitive slowing. More focal (specific) symptoms could include difficulties with hearing, speech, ambulation, dexterity, visual difficulties, and mood disturbances. These symptoms can have a profound effect on the quality of life of the patient as well as their ability to work and to care for themselves. A significant physical and emotional burden is often placed on carers, particularly as the disease progresses.

2.5 Treatment of malignant glioma varies from country to country. In the UK, about 30% of patients receive only supportive care with steroids, with or
without anticonvulsants.

2.6 More intensive treatment is offered to patients with less severe disability, measured on the Karnofsky scale (Karnofsky performance status > 60): see appendix D for details. The tumour is removed as far as possible, but can usually not be fully excised because of the infiltrative nature of these tumours. The remaining tumour tissue undergoes radical radiotherapy. The whole procedure adds some 4 to 5 months to median survival. In the USA, chemotherapy is routinely given 6 weeks after radiation (adjuvant chemotherapy), but this is not the practice in the UK or Europe.

2.7 The great majority (at least 70%) of malignant gliomas recur locally after initial treatment, usually with very disabling neurological deficit and poor and rapidly deteriorating quality of life. Options for further treatment at this stage are limited and palliative. In the UK and Europe, clinical or imaging evidence of tumour progression after radiation therapy is employed as indication for first line chemotherapy.

2.8 For a patient whose tumour recurs or progresses following surgery/radiotherapy, the chemotherapy treatment options are limited because the currently available agents have only a small chance of being effective. Although high dose oral procarbazine is used as a single agent in the USA, it is not usual in the UK except in combination with lomustine and vincristine (PCV) regimen. This currently constitutes standard first line chemotherapy. Lomustine alone is sometimes used as first line therapy. The likelihood of response depends on age, tumour type and Karnofsky performance status (see appendix D). In general anaplastic astrocytoma (AA) is more responsive to chemotherapy than glioblastoma multiforme (GBM).

2.9 Current UK practice is to give first line chemotherapy to less than one third of patients whose tumour recurs after initial treatment, or about 15% of all diagnosed cases of brain tumour. This represents about 500 to 600 new cases per year.

2.10 Chemotherapy is given in cycles. PCV is given for 28 consecutive days in 56-day cycles, or for 21 consecutive days in 42-day cycles, usually for a maximum of 6 cycles. Therapy is usually stopped after 2 cycles in those
who do not respond (based on both clinical and radiological monitoring) and in those who experience significant toxicity. Usual outcome measures include clinical response, imaging parameters, side effect profile, progression free survival, overall survival and quality of life.

2.11 A meta-analysis of 10 randomised controlled trials (RCTs) of chemotherapy for glioma shows that mean survival time increases by 2 months (Confidence Interval 1 to 3 months) and that there are a number of other similarly small but significant improvements on other outcomes after chemotherapy.
3 The Technology

3.1 Temozolomide (Temodal) is an alkylating agent derived from dacarbazine and first synthesised in 1984. It is indicated for the treatment of patients with malignant glioma showing recurrence or progression after standard therapy. It is easier to administer than other chemotherapeutic regimes for this indication and is given orally once a day for 5 days in a 28-day cycle. It has high bioavailability and crosses the blood-brain barrier where it is spontaneously hydrolysed to its active form. It is toxic to cancer cells due to inhibition of tumour cell DNA replication.

3.2 It exhibits a broad spectrum of anti-tumour activity in animals and man. Side effects are less than existing regimes and include nausea, vomiting, fatigue and headache. Haematological toxicity is mild and non-cumulative.

3.3 Dosage in chemotherapy-naïve patients is 200 mg per square metre of patient surface area per day (i.e. generally averaging 340 mg per day). In patients previously treated with cytotoxic drugs, the dose is usually reduced by 25%.

3.4 The current UK price of this drug is £1,176 per 5-day cycle for a daily dose of 340 mg for those who have not had prior chemotherapy, and £934 for those who have.
4 Evidence

4.1 Clinical effectiveness

4.1.1 There has been only one randomised controlled trial (RCT) (of 225 patients) involving temozolomide versus procarbazine alone in patients with recurrent glioblastoma multiforme (GBM). There are no trials of temozolomide in anaplastic astrocytoma (AA). All patients in the GBM trial had received radiotherapy and two-thirds had also received first-line nitrosourea-based chemotherapy. Patients were required to have a histologically proven supratentorial GBM or gliosarcoma at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status \( \geq 70 \) and a projected life expectancy of \( \geq 12 \) weeks at entry.

4.1.2 Progression-free survival in the RCT at 6 months was 21% for those on temozolomide, compared with 8% for those on procarbazine (a statistically significant difference, \( p = 0.008 \)). The 6-month survival was 60% for temozolomide and 44% for procarbazine (also a significant difference, \( p = 0.019 \)), however the median survival advantage of 6 weeks in favour of temozolomide was not statistically significant.

4.1.3 Procarbazine alone is rarely if ever used in first line therapy in the UK and a more appropriate control arm for the UK might have been PCV (procarbazine with lomustine and vincristine) or lomustine alone. As this comparison has not been carried out, there is no direct evidence that temozolomide is more effective than a current UK standard treatment.

4.1.4 Six preliminary or phase II single-group studies each with over 40 patients, and several smaller such studies have been undertaken. The main results are that about 5% of GBM patients show a partial response to temozolomide (aggregate tumour volume halved) and for some 30% to 40% the disease exhibited no progression for a period of time. In other forms of malignant glioma about 10% show a complete response to temozolomide (disappearance of all enhancing tumours in neuroimaging), a further 25% a partial response and about 30% exhibit a period of no
Importantly for an incurable condition such as GBM, the quality of life for patients on temozolomide improves significantly prior to the onset of further disease progression, though it deteriorates rapidly thereafter. A similar trend is apparent following recurrence of other malignant gliomas but the evidence is less robust.

4.2 **Cost effectiveness**

4.2.1 There is insufficient evidence to assess the clinical effectiveness of temozolomide as first-line chemotherapy. Therefore its cost-effectiveness in this indication has not been considered any further.

4.2.2 Where first-line chemotherapy with PCV has failed, temozolomide should be compared with the only alternative, which is best supportive care. However, the only data compares the benefits of temozolomide with those of procarbazine alone. Costs per cycle of temozolomide are estimated to be £1,488 including hospital costs and medications for side effects.

4.2.3 Estimating cost per quality adjusted life year (QALY) is difficult because the extension of median survival time is not statistically significant, and the quality of life data are limited. The main benefit of temozolomide is that a proportion of patients benefit from a longer progression free survival time. Therefore the most useful measure of cost-effectiveness is cost per progression free week. Costs will continue to accrue if patients remain progression free, because further cycles of the drug will be given until progression occurs.

4.2.4 For glioblastoma multiforme (GBM), the median estimate of progression-free survival, using temozolomide was 12.4 weeks, and using procarbazine, 8.3 weeks (a difference of 4.1 weeks, p = 0.006). The incremental cost of temozolomide against procarbazine was £4,044, giving an incremental cost per progression-free week of £1,000. The cost per progression-free week for temozolomide against placebo (assuming the placebo would have no cost and no effect) would have been £400.
4.2.5 For anaplastic astrocytoma (AA), the figures are more uncertain than for GBM, as there is no RCT on which to base estimates, only single group studies. On the basis that for temozolomide the median estimate of progression free survival is 11 weeks in AA, and that none of this is a placebo effect, the cost per progression-free week would be £410.

4.2.6 For GBM, the costs per life year gained are as follows. For an estimated gain in median progression free survival of 4.1 weeks associated with a gain in total survival of 6 weeks, and for no incremental gain in utility due to an improved quality of life, the incremental cost per life year gained of temozolomide against procarbazine for GBM is estimated to be £35,000. The cost per life year gained of temozolomide for GBM against PCV is not known.

4.2.7 For AA, assuming an estimated gain in progression free survival of 11 weeks and in total overall survival of 12 weeks, with no incremental gain in utility due to an improved quality of life, and assuming no placebo effect, the cost per life-year gained of temozolomide is estimated to be £35,000. The cost per life-year gained of temozolomide for AA against PCV is not known.

4.2.8 Whilst the indirect and informal costs of malignant glioma may be substantial, the change in these costs when temozolomide is introduced is unlikely to be large. Therefore the costs per unit of benefit will not alter to any extent from those reported above when these costs are included in the calculations.
5 Implications for the NHS

5.1 Currently, chemotherapy is used for about 500 to 600 people with recurrent malignant glioma per year. The number of patients for whom first line chemotherapy fails and whose condition will allow sufficient benefit from temozolomide as a second-line therapy is likely to be only a small proportion of these, perhaps 25%. It is therefore assumed that 150 patients per year would be eligible for temozolomide treatment under this guidance. If they were to receive an average of 4 cycles, the incremental cost would be about £6,400 per person. This would amount to about £1 million in aggregate, per year, for the NHS.

5.2 Other impacts on the NHS would be small. If total survival were to increase by the same amount as the progression-free period, then a small increase in total NHS costs could be expected.
6 **Further Research**

6.1 A randomised controlled trial of temozolomide against PCV is needed (and planned by the Cancer Research Campaign) for those with relapsed glioblastoma multiforme (GBM), anaplastic astrocytoma (AA) and other malignant gliomas. It should have sufficient power to detect a two-month difference in median survival time, and particular emphasis should be placed on quality of life measurement with sufficient detail on key symptoms (e.g. headache, epileptic fits, rate of cognitive decline) for robust comparisons to be made.

6.2 Studies of temozolomide in combination chemotherapy (including at least one with an agent which diminishes the repair enzyme AGT O6-alkylguanine-DNA-alkyltransferase) against other classes of chemotherapy drugs would be valuable.

6.3 Research into the effect of the drug on children is required.
7 Implementation

7.1 NHS trusts with responsibility for treating people with recurrent malignant glioma (brain cancer) should enable clinicians to consider the option of using temozolomide as set out in section 1.

7.2 Clinicians with responsibility for treating people with recurrent malignant glioma (brain cancer) should review their current practice in line with the guidance set out in section 1.

7.3 The patient information attached to this guidance as appendix C can be drafted into local information leaflets as advice for people with recurrent malignant glioma (brain cancer) and those who care for them.

7.4 To enable clinicians to audit their own compliance with this guidance it is recommended that treatment plans are recorded for each patient.

7.5 This information should be incorporated into local audit data recording systems and consideration given (if not already in place) to the establishment of appropriate categories in routine electronic record keeping systems used in hospitals and the multi-disciplinary groups working in support of people with recurrent malignant glioma (brain cancer).

7.6 Relevant clinical guidelines and protocols linking the multi-disciplinary working for people with recurrent malignant glioma (brain cancer) should be reviewed in the light of this guidance.

7.7 Prospective clinical audit programmes should record the proportion of treatments adhering to this guidance. Such programmes are likely to be more effective in improving patient care when they form part of the organisation's formal clinical governance arrangements and where they are linked to specific post-graduate activities.
8 Review of Guidance

8.1 Information on the review of the guidance on this technology is available on the NICE website.

Andrew Dillon
Chief Executive
April 2001
Appendix A. Appraisal Committee Members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The committee are supplemented by technology specific experts as indicated in appendix B.

Dr Jane Adam
Radiologist, St George's Hospital, London

Dr Sunil Angris
General Practitioner, Waterhouses Medical Practice

Professor David Barnett (Chair)
Professor of Clinical Pharmacology, University of Leicester

Professor Carol Black
Consultant Physician, Royal Free Hospital & UCL, London

Professor John Brazier
Health Economist, University of Sheffield

Professor Bruce Campbell
Consultant Surgeon, Royal Devon & Exeter Hospital

Professor Mike Campbell
Statistician, Institute of General Practice & Primary Care, Sheffield

Dr Karl Claxton
Health Economist, University of York

Professor Jack Dowie
Health Economist, London School of Hygiene & Tropical Medicine, London

Dr Paul Ewings
Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23)

Statistician Taunton & Somerset NHS Trust

Sally Gooch
Director of Nursing, Mid-Essex Hospital Services Trust

Liz Heyer
Chief Executive, Barnet & Chase Farm Hospitals NHS Trust

Dr Diane Ketley
Research into Practice Programme Leader, NHS Modernisation Agency

Ruth Lesirge
Patient Representative; Director, Mental Health Foundation

Dr George Levvy
Patient Representative; Chief Executive, Motor Neurone Disease Association

Dr Gill Morgan
CEO, North & East Devon Health Authority

Professor Miranda Mugford
Health Economist, University of East Anglia

Siân Richards
General Manager, Cardiff Local Health Group

Professor Philip Routledge
Professor of Clinical Pharmacology, University of Wales

Dr Rhiannon Rowsell
Pharmaceutical Physician, AstraZeneca UK Ltd

Dr Stephen Saltissi
Consultant Cardiologist, Royal Liverpool University Hospital

Professor Andrew Stevens
Professor of Public Health, University of Birmingham
Appendix B. Sources of Evidence

1. The following documentation and opinion was made available to the Committee:

a. Assessment Report:

   • prepared by Wessex Institute for Health Research and Development, University of Southampton (The effectiveness and cost effectiveness of temozolomide for the treatment of recurrent malignant glioma, November 2000).

b. Manufacturer/sponsor submissions:

   • Schering Plough UK Ltd

c. Professional/specialist group, patient/carer group and trade association submissions:

   • Royal College of Physicians and the Royal College of Radiologists (joint)
   • MRC Clinical Trials Unit
   • Royal College of General Practitioners
   • Royal College of Surgeons of England
   • Association of British Neurologists and the Royal College of Physicians (joint)

d. External expert and patient advocate submissions:

   • Dr Paul Symonds, Reader and Consultant in Clinical Oncology, University of Leicester
   • Douglas Guerrero, Clinical Nurse Specialist/Neuro-Oncology, Royal Marsden Hospital
   • Dr Mike Brada, Reader and Consultant in Clinical Oncology, Royal Marsden Hospital
Appendix C. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) – Information for Patients

A summary of this guidance for patients and carers can be found on our website.
## Appendix D. Karnofsky Performance Score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>The patient has no complaints and is without evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>The patient has minor signs/symptoms, but is able to carry out his or her normal activities</td>
</tr>
<tr>
<td>80</td>
<td>The patient demonstrates some signs/symptoms and requires some effort to carry out normal activities</td>
</tr>
<tr>
<td>70</td>
<td>The patient is able to care for self, but is unable to do his or her normal activities or active work</td>
</tr>
<tr>
<td>60</td>
<td>The patient is able to care for self, but requires occasional assistance</td>
</tr>
<tr>
<td>50</td>
<td>The patient requires medical care and much assistance with self care</td>
</tr>
<tr>
<td>40</td>
<td>The patient is disabled and requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>The patient is severely disabled and hospitalisation is indicated; Death is not imminent</td>
</tr>
<tr>
<td>20</td>
<td>The patient is very ill with hospitalisation and active life-support treatment necessary</td>
</tr>
<tr>
<td>10</td>
<td>The patient is moribund with fatal process proceeding rapidly</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

### ECOG/WHO/RTOG to KPS (Approximate Conversion System)

<table>
<thead>
<tr>
<th>E/W/R</th>
<th>Karnofsky</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90–100%</td>
<td>Normal activity</td>
</tr>
<tr>
<td>1</td>
<td>70–80%</td>
<td>Symptoms demonstrated, but the patient remains ambulatory, and able to perform self-care</td>
</tr>
<tr>
<td>2</td>
<td>50–60%</td>
<td>Ambulatory &gt;50% of the time and requires occasional assistance</td>
</tr>
<tr>
<td>3</td>
<td>30–40%</td>
<td>Ambulatory &lt;50% of the time and requires nursing care</td>
</tr>
<tr>
<td>4</td>
<td>10–20%</td>
<td>Bedridden</td>
</tr>
</tbody>
</table>
Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
Appendix E. The new WHO Classification of Tumours affecting the Central Nervous System

In 1993 the WHO ratified a new comprehensive classification of neoplasms affecting the central nervous system. The classification of brain tumours is based on the premise that each type of tumour results from the abnormal growth of a specific cell type. To the extent that the behaviour of a tumour correlates with basic cell type, tumour classification dictates the choice of therapy and predicts prognosis. The new WHO system is particularly useful in this regard with only a few notable exceptions (for example all or almost all gemistocytic astrocytomas are actually anaplastic and hence grade III or even IV rather than grade II as designated by the WHO system). The WHO classification also provides a parallel grading system for each type of tumour. In this grading system most named tumours are of a single defined grade. The new WHO classification provides the standard for communication between different centres around the world. An outline of this classification is provided below.

Neuroepithelial Tumors of the CNS (first five main types)

I. Astrocytic tumours [glial tumours — categories I–V, below — may also be subclassified as invasive or non-invasive, although this is not formally part of the WHO system, the non-invasive tumour types are indicated below. Categories in italics are also not recognized by the new WHO classification system, but are in common use.]

1. Astrocytoma (WHO grade II)
   a. variants: protoplasmic, gemistocytic, fibrillary, mixed

2. Anaplastic (malignant) astrocytoma (WHO grade III)
   a. hemispheric
   b. diencephalic
c. optic
d. brain stem
e. cerebellar

3. Glioblastoma multiforme (WHO grade IV)
a. variants: giant cell glioblastoma, gliosarcoma

4. Pilocytic astrocytoma [non-invasive, WHO grade I]
a. hemispheric
b. diencephalic
c. optic
d. brain stem
e. cerebellar

5. Subependymal giant cell astrocytoma [non-invasive, WHO grade I]

6. Pleomorphic xanthoastrocytoma [non-invasive, WHO grade I]

II. Oligodendroglial tumors

1. Oligodendroglioma (WHO grade II)

2. Anaplastic (malignant) oligodendroglioma (WHO grade III)

III. Ependymal cell tumours

1. Ependymoma (WHO grade II)

   a. variants: cellular, papillary, epithelial, clear cell, mixed
2. Anaplastic ependymoma (WHO grade III)

3. Myxopapillary ependymoma

4. Subependymoma (WHO grade I)

IV. Mixed gliomas

1. Mixed oligoastrocytoma (WHO grade II)

2. Anaplastic (malignant) oligoastrocytoma (WHO grade III)

3. Others (e.g. ependymo-astrocytomas)

V. Neuroepithelial tumours of uncertain origin

1. Polar spongioblastoma (WHO grade IV)

2. Astroblastoma (WHO grade IV)

3. Gliomatosis cerebri (WHO grade IV)

A number of grading systems are in common use for tumours of astrocytic lineage (i.e. astrocytomas, anaplastic astrocytomas and glioblastomas). Grades are assigned solely based on the microscopic appearance of the tumour. The numerical grade assigned for a given tumour, however, can vary depending on which grading system is used as illustrated by the following table. Thus, it is important to specify the grading system referred to when a grade is specified. The St. Anne/Mayo grade has proven to correlate better with survival than the previously common Kernohan grading system. It can only be applied to invasive tumours of astrocytic lineage; it is otherwise similar to the WHO grading system.

<table>
<thead>
<tr>
<th>Grading of astrocytic tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO designation</td>
</tr>
<tr>
<td>pilocytic astrocytoma</td>
</tr>
</tbody>
</table>

Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) (TA23)
<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Grade</th>
<th>Grades</th>
<th>Count</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrocytoma</td>
<td>II</td>
<td>I, II</td>
<td>1</td>
<td>No criteria fulfilled</td>
</tr>
<tr>
<td>Anaplastic (malignant) astrocytoma</td>
<td>III</td>
<td>II, III</td>
<td>2</td>
<td>one criterion: usually nuclear atypia</td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>IV</td>
<td>III, IV</td>
<td>3</td>
<td>two criteria: usually nuclear atypia and mitosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>three or four criteria: usually the above and necrosis and/or endothelial proliferation</td>
</tr>
</tbody>
</table>

* The WHO and Kernohan systems are not criteria based. Thus, a given tumour may not fall under the same designation in all three systems.
Update information

**March 2016**: The wording of recommendation 1.1 has been updated in line with NICE's wording conventions.

Recommendations 1.2 and 1.3 for temozolomide for the first-line chemotherapy treatment of malignant glioma when primary therapy (surgery and/or radiotherapy) has failed have been updated by recommendation 1.1 of NICE's technology appraisal guidance on carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma.
About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance 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.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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ISBN: 978-1-4731