



*National Institute for
Clinical Excellence*

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Clinical Excellence***

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

This document has been circulated to the following:

- Health Authority Chief Executives in England and Wales
- NHS Trust Chief Executives in England and Wales
- PCG Chief Executives
- Local Health Group General Managers
- Medical and Nursing Directors
- Consultant Oncologists in England and Wales
- Consultant Neurologists and Neurological Surgeons in England and Wales
- Chief Pharmacists, Heads of Drug Purchasing, Heads of Drug Information, Pharmaceutical Advisors, GP Prescribing Advisors and Purchase Advisors in England and Wales
- NHS Director Wales
- Chief Executive of the NHS in England
- NHS Executive Regional Directors
- Special Health Authority Chief Executives
- Community Health Councils in England and Wales
- Patient advocacy groups
- Commission for Health Improvement
- NHS Clinical Governance Support Team
- Chief Medical and Nursing Officers in England and Wales
- Medical Director & Head of NHS Quality – National Assembly for Wales
- Clinical Effectiveness Support Unit - Wales
- Representative bodies for health services, professional organisations and statutory bodies, Royal Colleges

This Guidance is written in the following context:

This guidance represents the view of the Institute which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgment. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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

1. Guidance

- 1.1 Patients with recurrent malignant glioma (brain cancer) who have failed first-line chemotherapy treatment with other agents (either because of lack of efficacy or because of side effects) may be considered for treatment with temozolomide. Such patients must have a histologically proven malignant glioma (WHO grades III and IV, or transformed grade II) at first relapse, recurrence or progression (as assessed by imaging), Karnofsky performance status greater than or equal to 70 and a projected life expectancy of 12 weeks or more, at initiation of temozolomide treatment. (See Appendix D for definition of Karnofsky status and Appendix E for definition of WHO tumour grading).
- 1.2 Temozolomide is not recommended for first-line chemotherapy treatment for patients with malignant glioma who have failed primary therapy (surgery and/or radiotherapy), except in the context of a randomised controlled trial against a standard-treatment comparator.
- 1.3 As temozolomide is not currently licensed for adjuvant chemotherapy treatment of malignant glioma, its use in this indication has not been considered in this appraisal.

This section (Section 1) constitutes the Institute's Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer). The remainder of the document is structured in the following way:

2 Clinical Need	8 Review of Guidance
3 The Technology	Appendix A: Appraisal Committee
4 Evidence	Appendix B: Sources of Evidence
5 Implications for the NHS	Appendix C: Information for Patients.
6 Further Research	Appendix D: Karnofsky Performance Score
7 Implementation	Appendix E: WHO Classification

The full document and a Summary of Evidence are available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number 23698.

Mae'r adran hon (adran 1) hefyd ar gael yn Gymraeg ar ein gwefan neu drwy gysylltu â 0870 1555 455, rhif cyfeirnod 23699.

- 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 regimens 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 ≥ 70 and a projected life expectancy of ≥ 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 neuro-imaging), a further 25% a partial response and about 30% exhibit a period of no progression.

- 4.1.5 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.

7

Implementation

- 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.
- 7.1 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 This Guidance will be reviewed in March 2004.

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

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

Professor John Brazier

Health Economist
University of Sheffield

Professor Bruce Campbell

Consultant Surgeon
Royal Devon & Exeter Hospital

Professor Mike Campbell

Statistician
Inst. of General Practice & Primary
Care, Sheffield

Dr Karl Claxton

Health Economist
University of York

Professor Jack Dowie

Health Economist
School of Hygiene & Tropical
Medicine

Dr Paul Ewings

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

Clinical Governance Programme
Leader
Leicester Royal Infirmary

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

Professor Ray Tallis

Consultant Physician
Hope Hospital, Salford

Professor Mary Watkins

Professor of Nursing
University of Plymouth

Dr Norman Waugh

Public Health Consultant
University of Southampton

Dr Fay Wilson

General Practitioner
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

The patient information in this appendix has been designed to support the production of your own information leaflets; you can download it from our web site (www.nice.org.uk) where it is available in English and Welsh. A printed version of this text is available in English/Welsh or English alone. If you would like copies of the printed leaflet please contact 0870 1555 455, and quote the reference number 23701 for the English/Welsh version and 23700 for the English only version.

What is NICE Guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment, diagnostic tests and clinical & surgical procedures and where they should be used.

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations and the groups who represent patients.

NICE was asked to look at the available evidence on temozolomide and provide guidance that would help the NHS in England and Wales decide where it should be used in the treatment of recurrent malignant glioma (brain cancer).

What is malignant glioma?

Malignant glioma is the most common form of brain tumour. In England and Wales. It affects about 4 people in 100,000 and there are about 3,500 new cases in the UK each year. Brain tumours account for only 2 in 100 cancer deaths. Just over half the first time brain cancers occur in men. Around 29 out of 100 adults with this type of cancer survive one year after diagnosis and 13 out of 100 survive 5 years.

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, loss of appetite, feeling sick, vomiting, seizures, drowsiness, personality changes, and a slowing down of mental processes such as knowing, thinking, learning and making judgements. More specific symptoms could include difficulties with hearing, speech, walking, dexterity, seeing difficulties, and mood disturbances. These symptoms can have a profound effect on the quality of life of the person with the cancer 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.

Treatment of malignant glioma varies from country to country. In the UK, about 3 out of 10 people with brain cancer receive only supportive care with steroids, with or without anticonvulsants.

More intensive treatment is offered to patients with less severe disability. The tumour is removed as far as possible, but can usually not be fully removed because the tumour infiltrates surrounding tissues. The remaining tumour tissue undergoes radiotherapy (treatment with radiation therapy). The great majority (at least 7 out of 10) of malignant gliomas recur (come back) after this initial treatment. Options for further treatment at this stage are limited and offer symptom relief, not a cure for the cancer. Evidence that the tumour is progressing (growing) after this radiation therapy is used as a sign that it may be appropriate to start chemotherapy (this is known as 'first-line' chemotherapy treatment).

The chemotherapy treatment options are limited because the currently available agents have only a small chance of being effective. High dose oral procarbazine is often used in combination with lomustine and vincristine as the standard first line chemotherapy. This may be referred to as a PCV regimen. Lomustine is sometimes used alone as first line therapy. The likelihood of response depends on age, tumour type and how well the patient was when they started treatment.

Currently about one third of people who's tumour recurs after initial treatment are suitable for first line chemotherapy. This means about 500 to 600 people per year.

What is Temozolomide?

Temozolomide (Temodal) is a chemotherapy treatment which is given by the mouth once a day for 5 days out of 28. It is toxic to cancer cells because it crosses from the blood supply into the brain where it stops a part of the cancer cell replicating itself. Side effects include nausea, vomiting, fatigue and headache.

What has NICE recommended about the use of Temozolomide?

People with recurrent brain cancer whose initial chemotherapy treatment has failed (either because it was not effective or because it caused side effects) may be considered for treatment with temozolomide, when:

- they have a tumour that has been shown to be malignant through microscopic examination of the tumour cells (at first relapse);
- imaging tests have shown that the tumour has re-occurred or is progressing (imaging tests are used to produce pictures of areas inside the body);
- they have a Karnofsky performance status greater than or equal to 70 (Karnofsky is a measure given by a health professional to a patient's ability to perform certain ordinary tasks: 100 = normal, no complaints, 70 = unable to carry on normal activity, 50 = requires considerable assistance, 40 = disabled, 30 = hospitalisation recommended);

- it is expected that they will live for 12 weeks or more, at the start of the temozolomide treatment.

Temozolomide is only recommended as the initial chemotherapy treatment for patients with brain cancer when they are taking part in a clinical trial.

What should I do?

If you, or someone you care for, has brain cancer then you can discuss this advice with the doctor or nurse at your next appointment.

Will NICE review its Guidance?

Yes. The guidance will be reviewed in March 2004.

Further Information

Further information on NICE, and the full guidance issued to the NHS is available on the NICE web site (www.nice.org.uk).

The guidance can also be requested from 0870 555 455, quoting reference 23698.

If you have access to the Internet and would like to find out more about cancer visit the NHS Direct website: www.nhsdirect.nhs.uk.

APPENDIX D

Karnofsky Performance Score

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

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

E/W/R	Karnofsky	Details
0	90-100%	Normal activity
1	70-80%	Symptoms demonstrated, but the patient remains ambulatory, and able to perform self care
2	50-60%	Ambulatory >50% of the time and requires occasional assistance
3	30-40%	Ambulatory <50% of the time and requires nursing care
4	10-20%	Bedridden
5	0%	Death

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)
 1. variants: protoplasmic, gemistocytic, fibrillary, mixed
 2. Anaplastic (malignant) astrocytoma (WHO grade III)
 1. hemispheric
 2. diencephalic
 3. optic
 4. brain stem
 5. cerebellar
 3. Glioblastoma multiforme (WHO grade IV)
 1. variants: giant cell glioblastoma, gliosarcoma
 4. Pilocytic astrocytoma [non-invasive, WHO grade I]
 1. hemispheric
 2. diencephalic
 3. optic
 4. brain stem
 5. 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)
 - 1. 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.

Grading of astrocytic tumours				
WHO designation	WHO grade*	Kernohan grade*	St. Anne/Mayo grade	St. Anne/Mayo criteria
pilocytic astrocytoma	I	I	excluded	-
astrocytoma	II	I, II	1	no criteria fulfilled
			2	one criterion: usually nuclear atypia
anaplastic (malignant) astrocytoma	III	II, III	3	two criteria: usually nuclear atypia and mitosis
glioblastoma	IV	III, IV	4	three or four criteria: usually the above and necrosis and/or endothelial proliferation

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