Clinical Practice Guidelines

for the management of adult gliomas: astrocytomas and oligodendrogliomas

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Conflict of interest

The development of these clinical practice guidelines has been undertaken by a non-remunerated Working Party of the Australian Cancer Network, with the assistance of a generous private donation.

Some members of the Working Party have received sponsorship to attend scientific meetings, been supported in the conducting of clinical trials or have been involved in an advisory capacity by pharmaceutical and biochemical companies.

The Australian Cancer Network holds a register of conflict of interest.

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Disclaimer

This document is a general guide to appropriate practice, to be followed only subject to the clinicians' judgement in each individual case.

The recommendations are designed to provide information to assist decision-making and are based on the best information available at the date of compilation. The guide is not meant to be prescriptive.

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PREFACE

This publication will be of great value to the brain tumour patient, their family and caregivers in Australia because it will set out the type of treatment that a patient should receive, taking into account their tumour and individual health situation.

It provides a documented benchmark which the interested health care consumer can consult to check whether their treatment accords with what is regarded as standard therapy in the developed world. Let us not forget that many, if not most, of the 200,000 people who are diagnosed worldwide each year with a malignant primary brain tumour are unlikely to have access to even the minimum standard of care outlined in these pages.

On the other hand, significant sections of these Guidelines should be out of date as soon as they are published. That might sound odd but that is the only way we will advance towards a cure for these highly lethal tumours - ideally, new therapies and approaches will be discovered rapidly as we march towards a "cure" and not just palliation.

Hope has been generated by the choice of gliomas as one of the priority areas for attention under the human genome project and the unprecedented number of clinical trials for brain tumours, either from a company initiative or from an independent researcher. What has been discovered already is pointing towards a new era of combination and targeted therapies.

The journey with a brain tumour is not one that anyone undertakes in a voluntary capacity. It is enormously challenging, for the patient, their family and caregiver. One hopes that the information contained in these Guidelines will help to make that journey just a little easier.

On behalf of brain tumour consumers we offer our thanks to those who were involved with the drafting of this document and those who undertook the basic research in the hundreds of learned papers that provide the evidence base for its conclusions.

Denis Strangman

Consumer Representative
Brain Tumour Guidelines Working Party

Chair and Co-Director
International Brain Tumour Alliance IBTA

FOREWORD

Brain tumours are uncommon tumours but they have a devastating effect on patients' lives and the lives of their caregivers. Although malignant brain tumours make up only two percent of all cancers they result in the fourth highest loss of potential years of life.[1] On average a patient with a malignant brain tumour loses 12 years of potential life; the highest average loss of life from any type of cancer. Because of this, brain tumours cause the highest economic burden on Australian cancer patients' households, with an average cost estimated to be more than five times higher than for breast or prostate cancer patients.[2]

These guidelines have been developed to provide information on malignant adult brain tumours (specifically gliomas) to medical practitioners and interested community members. The aim is to direct attention to improve the level of practice and understanding in a health area that causes considerable community anxiety. Brain tumours also contribute heavily through costs of hospital, home and community management to the budget of the Australian health care system. They impose the highest economic burden on carers of any cancer, as well as significant emotional and physical challenges.

Guidelines for adult gliomas are needed because of the considerable variation in clinical practice. A patterns-of-care study in Victoria[3] has recently documented that only 74% of patients were referred for radiotherapy and only 54% saw a medical oncologist. Radiotherapy offers a major survival benefit but only 68% of patients with glioblastoma multiforme received radiotherapy. It is unlikely that one-third of patients were too unfit for treatment. There is no reason to believe that the situation is different in other Australian States.

It is a common misconception that there is not much evidence to support glioma management. This is far from the case; high-level randomised data exist from many trials of treatment and for many supportive interventions. Controversies exist and are best viewed in the light of systematically assembled evidence. Thus the necessary conditions exist for the development of guidelines; a high community burden, evidence of variation in practice and good evidence on optimum patient management.

These guidelines are for the management of adult gliomas including low- and high-grade gliomas (anaplastic astrocytoma, glioblastoma multiforme and oligodendroglioma). They encompass all aspects of patient management, not just treatment. A general approach to patients is suggested because it is recognised that a diagnosis of brain tumour can have profound implications. Clinical presentation, diagnostic work up and imaging are reviewed. Treatment is discussed separately for low-grade gliomas, high-grade gliomas and oligodendrogliomas.

Clinical trials are the major route for the development of new treatments, yet in the Victorian study[3], only 5% of patients participated in clinical trials. We present a chapter on clinical trials as a resource to encourage greater participation in trials.

A great many cancer patients seek further hope in complementary, alternative and unproven treatments. We provide some guidance on the range of treatments offered and some tools for the critical appraisal of complementary, alternative and unproven treatments.

We also present guidance about continuing care including psycho-social support, the management of symptoms, rehabilitation, follow-up and palliative care. Management is often complex because of the interaction of multiple medical problems and behavioural and psychosocial issues. We examine in detail the management of headaches, steroids and anti-convulsants and the current legal requirements about driving.

As with all of the Australian guidelines, these guidelines were produced by a group of experts who have donated their time and have spent many laborious hours reviewing the medical literature and conferring with their colleagues. We are especially grateful to Ms Christine Vuletich at the Australian Cancer Network for her unstinting efforts to collate and produce the finished guidelines document. As with all national cancer guidelines, the adult glioma guidelines have benefited greatly from the guidance, wisdom, persistence and energy of Emeritus Professor Tom Reeve who has steered the executive group through the very long process of guidelines development. These guidelines would not have been possible without them and the generous donation of Mr Steven Newton in memory of his wife Valerie. A consumer version and guidance for general practitioners will be prepared to follow these guidelines. We intend to publish these guidelines on-line as a wiki to facilitate wider dissemination and the rapid incorporation of new evidence.

References

1 Australian Institute of Health and Welfare and Australasian Association of Cancer Registries. Cancer in Australia 2001. Canberra: AIHW; 2004.

2 Access Economics. Cost of cancer in NSW. Sydney: Cancer Council NSW; 2006 Jun 15.

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Professor Michael Barton OAM
Chair, Brain Tumour Guidelines Working Party
Professor of Radiation Oncology, UNSW
Liverpool Cancer Therapy Centre
Locked Bag 7103
Liverpool BC NSW 1871
Email: Michael.Barton@sswahs.nsw.gov.au

Dr Elizabeth Hovey
Project Officer, Brain Tumour Guidelines Working Party
Senior Staff Specialist
Department of Medical Oncology
Prince of Wales Hospital
Level 2, High Street
Randwick NSW 2031
Email: Elizabeth.Hovey@sesiahs.health.nsw.gov.au

SUMMARY OF RECOMMENDATIONS AND KEY POINTS

(Levels of evidence and references shown for Recommendations only)

Key points and recommendations	Level of evidence	Refs
1. Setting the scene		
• Astrocytomas and oligodendrogliomas are the largest groups of gliomas, which are primary CNS cancers. • Primary CNS cancers are diagnosed in 7/100,000 Australians each year, compared with colon cancer 60/100,000 per year. • Although uncommon, CNS cancers are associated with the highest potential years of life lost of all major cancers–on average 12 years per patient. • Most astrocytomas and oligodendrogliomas occur in the brain, with only 5% in the spinal cord. They have a tendency to progress to more malignant grades over time. • Gliomas are more common in males. Median age at diagnosis is 55-59 years in males, 60-64 years in females. • Incidence has increased slightly over the last twenty years, probably due to improved imaging and more investigation in elderly patients. • Incidence of glioma does not vary much between geographical areas. • Median survival after resection is five to eight years for low-grade astrocytoma, three years for patients with anaplastic astrocytoma, about one year for patients with GBM, up to ten years for low-grade oligodendroglioma and one to seven years for anaplastic oligodendroglioma. Younger age, good preoperative performance status and gross macroscopic resection are associated with longer survival. • Nearly all CNS cancers arise randomly. The only known cause is ionising radiation. • Known risk factors for developing glioma are increased age, male sex and rare familial genetic syndromes. • Except possibly for neurofibromatosis type 1, no screening test is available for glioma as early detection does not increase the benefit of treatment.		
2. Approach to the patient		
• The approach to the patient must include recognition of the concerns of family members and caregivers and incorporate attention to complex medical and psychosocial issues.		

Key points and recommendations	Level of evidence	Refs
• Cognitive deficits are common with gliomas and can impair patients' abilities to comprehend information and specifically their capacity to provide informed consent for treatment. In the area of shared decision making, the guiding principles should be to respect patients' autonomy and to act in the patients' best interests.		
• Good practice points: - Present information in a clear and unambiguous way. Avoid medical jargon and use lay terms where possible. - Encourage the patient to ask questions about any aspects of the treatment/s. - Elicit the patients' values and preferences. - Negotiate a treatment decision with the patient. - Where possible, include another person in the room during your consultation with the patient (essential if there is any degree of cognitive impairment). - Where possible, aim to discuss while the person is still competent to make decisions the sort of treatment and care they would like to receive if their illness progressed. - Ask the person to nominate a surrogate-decision maker should their condition deteriorate and encourage the patient to discuss their wishes about treatment with this person.		
3. Clinical trials and research		
• Eligible patients should be offered clinical trial participation or referred to a centre where clinical trial participation is available.		
• The ethical principles of written informed consent should be carefully considered in patients with cognitive impairment, receptive dysphasia, or impairment of judgment.		
• Multidisciplinary involvement in a trial management committee is recommended for clinical trials in gliomas.		
• The use of several corroborative endpoints such as six-month progression-free survival, radiological response, cognitive function, and health-related quality of life are recommended for clinical trials in gliomas, however overall survival is the most robust endpoint. • Validated tools should be used for measurement of neurocognitive function and health-related quality of life. • Clinical trials in glioma should include central review of histopathology and radiological endpoints. • Consideration should be given to collection of tissue for biobanking and at autopsy in clinical trials.		

Key points and recommendations	Level of evidence	Refs
Time to progression is a better surrogate for survival than objective radiological response and should be incorporated as an endpoint in clinical trials.	III	23
Patients in clinical trials should be stratified for known important prognostic factors.	III	9
Central specialised neuro-pathology review must be incorporated into therapeutic clinical trials in brain tumours.	II	14
Validated health-related quality of life (HRQL) tools are available and should be used where measurement of HRQL is planned.	III	25,26
4. Clinical presentation		
A patient with new onset or recurrent headache uncharacteristic for that patient should also be imaged, particularly if there are focal neurological symptoms and signs.	III	11,13, 14,17
• Patients presenting with a first seizure should have adequate neuro-imaging with MRI.		
• All patients who present with focal neurological symptoms (such as hemiparesis, dysphasia, dysarthria, neglect, hemianopia, dressing apraxia) require neuro-imaging to establish the cause of these symptoms.		
• Consider referral of patients with glioma to a clinical genetics service if the patient or their first- or second-degree relatives have features or family history suggestive of neurofibromatosis type 1 or tuberous sclerosis. • Consider referral of patients with high-grade gliomas to a Cancer Genetics Service/Familial Cancer Clinic if there is a personal or family history (first or second-degree relatives) of premenopausal breast cancer, sarcoma, acute leukaemia or paediatric cancer, especially where two or more of these other cancer types have occurred and where one or more cases have occurred before age 45. • Consider referral of patients with high-grade gliomas to a Cancer Genetics Service/Familial Cancer Clinic if there is a personal or family history (first- or second-degree relatives) of bowel, uterine, stomach, ovarian, biliary/pancreatic or small intestinal cancer or TCC of the upper ureter, especially where two or more cases of these other cancers have occurred, and/or where one or more of these have been diagnosed before age 50.		

Key points and recommendations	Level of evidence	Refs
5. Imaging		
• Neuro-imaging is an essential component of glial series tumour management. • CT and MRI form the mainstay of tumour imaging. • The main aims of imaging of brain tumours are to: - primarily diagnose or refine a suspected diagnosis - optimally localise the lesion - characterise the lesion - assess the lesion's secondary effects and complications - plan surgical and radiation treatment including the provision of input data for neuronavigation - quantify therapeutic response - recognise post-treatment progression and complications		
• CT (with or without the use of intravenous contrast) because of its ready availability is most often the first examination to reveal the possibility of an intracranial neoplasm. • CT also helps also with the assessment of calcified and haemorrhagic lesions as well as those that may involve bone. • CT requires the use of x-rays (ionising radiation). • Contrast-enhanced MRI is the imaging modality of choice for the diagnostic workup of an intracranial lesion because of its superior soft tissue resolution and multi-planar imaging capabilities. • MRI has a greater accuracy in lesion depiction compared with CT. • MRI is contraindicated in patients with ferromagnetic aneurysm clips, cardiac pacemakers, cochlear implants and intra-orbital metallic foreign bodies.		

Key points and recommendations	Level of evidence	Refs
• No combination of clinical symptoms and signs reliably differentiate brain tumours from benign causes. • MRI and CT cannot reliably predict tumour type; biopsy and histological assessment are required. • Standardised tumour imaging protocols are necessary. • The timing of imaging must be appropriate to the patient's clinical state. • Scanning should be supervised by an accredited MRI and/or neuro-radiologist. • Ideally, all scans performed outside of the neurosciences centre should be reviewed by the neuro-radiological team prior to treatment. • Gliomas, particularly high-grade lesions, are heterogeneous structurally and are disseminated at the time of diagnosis. • Contrast-enhancing portions may either over- or under-estimate the presence of active tumour. • Low-grade glioma (LGG) will grow slowly in size, with a significant proportion undergoing anaplastic progression.		
• Glial tumours can have imaging characteristics that allow diagnosis and an estimation of pathological grade, however there is significant overlap and inconsistencies that limit accuracy of diagnosis. Biopsy is therefore required. • The appearances of brain stem and optic pathway gliomas may be very typical and given the risks of biopsy, treatment is often commenced on the basis of imaging appearances alone.		
• Reporting of neuro-oncology should ideally be performed by neuro-radiologists. • The radiological report is a dynamic phenomenon and may change with additional clinical or ancillary information. • More structured and standardised reporting is recommended. • If there are features that warrant emergency management, this should be directly conveyed to the referring physician as soon as possible. • It is important to assess and document tumour response to treatment.		

Key points and recommendations	Level of evidence	Refs
• 'Neuronavigation' projects CT and/or MRI data into the operative field for better anatomical orientation, better defining of anatomical landmarks, better positioning of the craniotomy flap, and precise targeting of pathological structures and tumour margins during operative procedures. • Intra-operative MRI can compensate for brain shifts and therefore allows a better assessment of the extent of resection.		
• Reactive post-operative changes can be seen as early as 18 hours on MRI and can last for years. • Immediate post-operative imaging may help to differentiate between residual tumour, postoperative reactive changes and parenchymal damage as a result of treatment. • Contrast-enhanced MRI is more sensitive in detecting changes compared with CT, however it still has limitations, notably with high-grade non-enhancing lesions. • Adherence to standardised imaging protocols is advised to aid in the interpretation of subsequent follow-up studies.		

Key points and recommendations	Level of evidence	Refs
• The aim of follow-up imaging is to monitor for treatment response, tumour recurrence or progression and to assess for any possible treatment-related side effects. • No adequate data exist on the role of imaging in the monitoring of response to therapy of gliomas, but nevertheless, this forms a significant part of neuro-oncology imaging. • MRI is the best imaging modality for the follow-up of glial series tumours, however the optimal frequency of these studies is unknown. Based on neuro-oncology trials, apart from any immediate post-operative scan the first baseline examination is usually performed between six weeks and three months after the completion of definitive treatment, then at two to three month intervals. If the disease is found to be stable, the interval may be increased to six months. • The difficulty in distinguishing between changes that may indicate a response to treatment and those indicating progressive tumour growth are important limitations of follow-up imaging. • Follow-up neuro-oncology imaging protocols should be standardised. • A description of the lesion on follow-up studies should include an objective measurement of tumour size. • Radiation necrosis is an uncommon irreversible progressive necrotic mass which is often identical in appearance to that of progressive residual or recurrent HGG and exists more often in combination with residual tumour. No adequate data are available on the role of imaging in differentiating between tumour recurrence and therapy-related changes.		
• Forms of advanced MRI that have been applied to neuro-oncology include MR spectroscopy (MRS), diffusion imaging, perfusion imaging and fMRI. • Patho-physiological changes are the focus of these techniques in disease. • There is no high-level evidence indicating better outcomes or management cost --effectiveness when using these techniques.		

Key points and recommendations	Level of evidence	Refs
• With the availability of CT and MRI, the use of nuclear imaging studies for brain tumours is no longer routine. • The use of scintigraphy is limited to research protocols and some specific clinical indications in centres with appropriate expertise. • Thallium (^{201}Tl) is the most frequently used isotope in neuro-SPECT, and may be helpful in pre-operative grading of the lesion and differentiating between recurrent high-grade glioma and radiation-induced necrosis. • Fluorodeoxyglucose (^{18}F FDG) is the most commonly used isotope in neuro-PET. This may have a role in pre-operative grading, evaluating the extent of tumour infiltration, finding an appropriate site for biopsy, and detecting malignant transformation in low-grade lesions.		
6. Diagnosis and pathology		
• The histological diagnosis of brain tumours should be undertaken by a neuro-pathologist or by an appropriately trained anatomical pathologist with some experience in tumour neuropathology. • Ideally *all* tissue removed from the patient should be submitted for pathological examination, including aspirated material and the material from ultrasonic surgical aspirators. • A pathology report should include at least the following information: demographic and clinical data; a macroscopic description of the material received; a microscopic description; a diagnosis incorporating tumour type (astrocytic, oligodendroglial) and tumour grade; and identification of any prognostic and/or predictive factors. • A histological diagnosis should take precedence over tissue banking when the specimen is small.		
7. Low-grade astrocytomas		
• Definitive diagnosis cannot be made on imaging alone. The presence or absence of enhancement offers some guidance but is not absolutely specific. Non-enhancing tumours may be high grade. Enhancing tumours may be low grade.		
• If the patient has been informed of all the pros and cons of a conservative approach and elects to wait then this is reasonable. This option is especially applicable if the tumour is less than 10cm^3 in volume, diffuse on T2 MRI scan and in an eloquent area. • Once progression has been documented treatment should be offered before the onset of fixed neurological deficits.		

Key points and recommendations	Level of evidence	Refs
• Histological diagnosis may be unreliable because of sampling error. • Pre-operative MR imaging may have a closer correlation with survival than histological grading on biopsy.		
• There is definitely a role for attempted resection of a low grade astrocytoma (LGA). It should probably be done at the time of diagnosis for the following potential benefits: more accurate diagnosis, palliation of symptoms, extension of survival, reduced chance of malignant transformation and possible cure. • Recommendation of resection should be tempered if the tumour is diffuse, located in an eloquent area or less than 10cm^3 in volume. • Standard microsurgical techniques should be employed with the addition of stereotactic guidance if available. • Awake surgery or cortical mapping are optional but may reduce the incidence of post-operative neurological deficit if the aim of surgery is to palliate and secure a diagnosis rather than prolong life or achieve a cure.		
• When no other treatment can be offered and there is clear clinical and/or radiological progression, there is definitely a role for radiotherapy. In the post-surgical setting, its role is less well defined. If surgery offers relief of symptoms and halts progression, then adjuvant treatment can be reserved for progressive disease. If radiotherapy is given immediately after surgery, it will extend time to progression (TTP) but will not extend OS any longer than if given later when the disease progresses. The role of chemotherapy in the treatment of LGAs is unclear.		
8. High-grade astrocytomas		
A tissue diagnosis should be obtained in all patients with a suspected high-grade astrocytoma before commencing definitive treatment.	III	115
Anti-neoplastic treatment should not be offered without a tissue diagnosis unless biopsy is considered too dangerous.	III	90-100
Patients with high-grade astrocytoma should have surgery for tumour resection if safe as this extends survival when compared to biopsy alone.	II	125,126
Patients with high-grade astrocytoma should have surgery for maximal tumour resection, aiming for gross macroscopic resection if safe, as this extends survival when compared to biopsy, subtotal or partial resection.	II	127

Key points and recommendations	Level of evidence	Refs
Patients with high-grade astrocytoma who are over the age of 65 or have poor performance status should have surgery for tumour resection if they are fit for surgery, as this extends survival when compared to biopsy alone.	II	126
Patients with high-grade astrocytoma benefit from implantation of carmustine wafers at the time of surgical resection of tumour as they provide a modest survival benefit of 8 to 11 weeks.	I	139-141
Patients with recurrent high-grade astrocytoma, particularly younger, asymptomatic patients, may benefit from resection of tumour.	III	156,161-166,168
Surgery for patients with high-grade astrocytomas should be conducted in accredited facilities complying with all relevant State, Federal, professional and educational policies, standards and guidelines.	III	156,161-166,168
Surgery for patients with high-grade astrocytomas should be conducted in a multidisciplinary environment with input from neuroradiology, intensive care, medical and radiation oncology, neuropathology, neurology, specialist surgery and nursing and allied health services.	III	156,161-166,168
Surgery for patients with high-grade astrocytomas should be conducted in a facility where an operating microscope, ultrasonic surgical aspirator and cortical mapping equipment are available.	III	156,161-166,168
Intra-operative frameless neuronavigation improves extent of resection and survival of patients with high-grade astrocytoma compared to unguided microsurgery, and its use is recommended.	III	178,180
Patients with high-grade astrocytoma should have radiotherapy because this extends median survival times when compared to no radiotherapy.	I	5,6,194, 195,198
Radiotherapy should start as soon as possible after a diagnosis of high-grade astrocytoma is established.	II	202, 203
The standard radiotherapy dose and fractionation schedule for patients with high-grade astrocytoma is 60Gy in 2Gy fractions and there is no evidence that higher doses improve outcome.	I	206-208
For adjuvant radiotherapy for high-grade astrocytoma, conventional fractionation (single daily fractions of 2Gy) is recommended. There is no evidence that hyperfractionation and/or accelerated fractionation improves outcome.	I	218, 219
Focal dose escalation with brachytherapy or stereotactic radiosurgery as part of initial radiotherapy for patients with high-grade astrocytoma does not improve outcome.	I	230

Key points and recommendations	Level of evidence	Refs
There is insufficient evidence to recommend short-course radiotherapy.	II	104
• Short-course low-dose radiotherapy may be suitable for patients with poor performance status who are keen to have treatment.		
For patients with high-grade astrocytoma, post-operative radiotherapy fields should include the tumour bed with a margin rather than the whole brain.	II	246,247
For radiotherapy for high-grade astrocytoma, involved field radiotherapy provides equivalent rates of local control and recurrence patterns to whole-brain radiotherapy.	III	230,251-253,263
The treatment volume or planning target volume (PTV) is defined as: - clinical target volume (CTV) + 5mm - CTV = Gross tumour volume (GTV) + high-signal area on T2-weighted MRI or perifocal hypodense zone on CT - GTV = contrast-enhancing area on CT or T1-weighted MRI	III	255
Both CT and MRI should be used for target volume delineation.	III	256,262
Histopathology remains the gold standard for diagnosis of radiation necrosis.	III	271
Adjuvant chemotherapy after surgery and radiotherapy provides modest improvement in progression free survival and overall survival for patients with GBM. However, adjuvant chemotherapy alone has been supplanted by concurrent chemo-radiotherapy followed by adjuvant chemotherapy and is thus not currently recommended.	I II	275 7
Adjuvant chemotherapy after surgery and radiotherapy improves disease free survival and is recommended for patients with anaplastic astrocytoma (AA).	I	271
Concurrent radiotherapy and chemotherapy followed by adjuvant chemotherapy provides a significant improvement in median and two-year survival in patients with GBM and is recommended.	II	7
• There are no data regarding either safety or efficacy of concurrent radiotherapy and chemotherapy followed by chemotherapy in patients with anaplastic astrocytoma and the regimen is not recommended.		7

Key points and recommendations	Level of evidence	Refs
• There are no data regarding concurrent radiotherapy and chemotherapy followed by chemotherapy in patients with ECOG performance status 3 or 4 and glioblastoma multiforme or anaplastic astrocytoma and the regimen is not recommended.		7
As there are insufficient data to make a recommendation for management with concurrent adjuvant radiotherapy and chemotherapy followed by chemotherapy in patients over 70 with glioblastoma multiforme or anaplastic astrocytoma, treatment decisions should be made on an individual basis.		277
Postoperative adjuvant temozolomide without radiotherapy is safe and tolerable in patients over age 70 with good performance status. Comparison of outcome with other regimens has not been made. Treatment decisions should be made on a case-by-case basis.	III	278
• There are no data regarding chemotherapy without radiotherapy for patients with high-grade astrocytoma and poor performance status and chemotherapy alone is not recommended as an alternative to radiotherapy.		277
Chemotherapy has modest activity in recurrent high-grade astrocytoma. A decision on its use should be made after discussion of risks and benefits, and consideration of other therapeutic options, but is generally recommended.	III	290-292
• The optimal duration of temozolomide treatment in patients with recurrent high-grade astrocytoma is not yet defined.		
9. Oligodendrogliomas		
• 1p/19q testing should be performed on all tumours with oligodendroglial features.		
All patients with suspected oligodendroglioma (OG) or oligoastrocytoma (OA) should undergo a biopsy for histological confirmation of tumour type and grade and to permit molecular analysis.	III	13,14
Maximal gross surgical resection is recommended where technically feasible, as this has been shown to increase survival.	IV	10,12
All suspected OGs / OAs must undergo histological confirmation as radiological features alone are inadequate for diagnosis and staging.	V	9,13
Observation only may be an acceptable strategy in grade II tumours with good prognostic features.	V	15
External beam radiotherapy is a standard treatment for OG and OA.	II	19, 20

Key points and recommendations	Level of evidence	Refs
The recommended radiotherapy dose is 50Gy in 2Gy fractions over six weeks.	II	19
Radiotherapy fraction size should not exceed 2Gy per day for high - dose treatments.	II	22–26
• Response to temozolomide chemotherapy correlates with 1p-/19q-.		
Adjuvant PCV chemotherapy is not recommended for high-grade OG and OA as standard therapy because there is no improvement in overall survival.	II	1, 31
• Chemotherapy-naive patients with high-grade oligodendroglioma who have recurred following radiotherapy will often respond to chemotherapy. • For recurrent high-grade OG, there may be a role for further chemotherapy and consideration of re-irradiation in patients with good performance status.		
10. Complementary, alternative and unproven therapy		
• There is no unifying definition of CAM and treatment that may fall within the definition of 'complementary', such as counselling, has high-level evidence to support its use. • There is evidence for an increasing interest in and use of CAM. • Antineoplastic activity of CAM in malignant glioma is supported by low-level evidence only, such as case reports, and cannot be recommended. • There needs to be a distinction between quality-of-life benefits and antineoplastic activity when assessing potential benefit. • Quality of life and/or symptom management such as control of nausea and vomiting with acupuncture are supported by good evidence. • Some of the modalities that may fall within the definition of CAM (eg counselling) are part of mainstream clinical practice and supported by high-level evidence.		

Key points and recommendations	Level of evidence	Refs
• There are potentially very important toxicities associated with CAM caused by interactions with conventional medicines and primary toxicity. • Many patients do not discuss CAM usage with their medical practitioner. • For malignant glioma there is no high-level evidence for antineoplastic activity of CAM. • Clinicians should enquire about the use of CAM in a non-confronting and non-judgemental way. • Health professionals should not participate in the administration of unproven anti-cancer treatments.		
11. Symptom management and complications		
Prophylactic anticonvulsants are not recommended. However, once started, an anticonvulsant is best withdrawn over several weeks.	I	1,6
Anticonvulsant treatment should be commenced after the first seizure in patients with gliomas.	II	14,15
If a decision to discontinue anticonvulsants is made, the drug should be withdrawn slowly, over two to three months.	I	1
Treatment with dexamethasone is recommended in patients who are symptomatic and have cerebral oedema. The usual starting dose is 16mg per day.	III	26
The dose of dexamethasone should be gradually tapered to the lowest amount that controls the patient's symptoms. Dexamethasone should not be discontinued abruptly.	III	26,28
Blood glucose concentrations, upper and lower limb power and weight should be assessed prior to starting corticosteroids and at regular intervals after treatment is started.	III	2
Treatment with a proton pump inhibitor is recommended if a patient receiving corticosteroids is also being treated with a NSAID or an anticoagulant, or if the patient has a past history of peptic ulcer disease.	I	2,26
Treatment with a proton pump inhibitor should be considered in patients receiving dexamethasone in a dose exceeding 16mg per day, or 16mg per day for a long interval.	I	2,26

Key points and recommendations	Level of evidence	Refs
Prophylactic treatment for osteoporosis should be started in post-menopausal women receiving corticosteroids and in pre-menopausal women and men if the T score is less than -1.5. The Australian Pharmaceutical Benefits Scheme currently approves the use of risedronate in patients on steroids for greater than three months with a T score of less than -1.	I	30
• When a new rash occurs in patients on anticonvulsants, liver and renal function should be checked to assess internal organ toxicity.		
Cutaneous drug eruptions with onset after 10 days of exposure to the drug, if associated with mucosal involvement or with systemic features, may be serious and require changing the antiepileptic medication to another group or category of drugs.	III	14
Either a nuclear scintigraphic ventilation-perfusion (V/Q) or a CT pulmonary angiogram can be used to diagnose pulmonary embolus. A 'low-probability' V/Q scan does not absolutely exclude the possibility of a pulmonary embolus.	I	47
The D-dimer, together with a careful clinical assessment, may be used to exclude a VTE and avoid unnecessary other investigations.	II	47
Perioperative thromboprophylaxis with a LMWH is recommended for most patients with gliomas, although subcutaneous UFH is a reasonable alternative unless there is evidence of haemorrhage.	I	61
Prophylaxis is particularly appropriate for patients with high-grade gliomas and in elderly and immobile patients.	I	41
Thromboprophylaxis should be interrupted for surgery (no LMWH for at least 24 hours prior to surgery), resumed during the post-operative period, and continue until the patient is fully mobile. Mechanical measures to avoid VTE are recommended as adjunctive therapy.	III	48,49
Anticoagulation with LMWH alone or followed by warfarinisation (for a period depending on the clinical scenario) is recommended as therapy for VTE in patients with gliomas. Exceptions may include anticoagulation in the immediate post-operative period, in which case a temporary IVC filter should be considered.	II	68
12. Psychosocial care		
Cognition dysfunction may not be apparent during brief consultations, and debilitating deficits will often only be detected by formal neuropsychological assessment undertaken by a trained health professional.	IV	14,15, 17,19

Key points and recommendations	Level of evidence	Refs
Health professionals should consider the need for formal neuropsychological assessment to determine the nature of cognitive deficits and provide a basis for recommendations regarding capacity to return to previous roles, and to assist the patient and their family to adjust.	IV	17
A medical practitioner must provide the patient with information to allow the patient to make an informed decision about treatment. A patient must be advised about the nature of their condition, any alternative forms of treatment that may be available, the consequences of those forms of treatment, and the consequences of remaining untreated.	I	27
It is up to the treating practitioner to determine whether a patient is competent to make a treatment decision.	I	27
Health professionals should determine the capacity of the patient to make decisions, and be aware of legislation that applies in the case of patients who are not competent to make decisions. Health professionals should be prepared to review this capacity as it may change over time.	I	27,29
• Cognitive and personality changes are common and have a powerful adverse impact on quality of life.		
Patients who have risk factors for increased psychological distress should be offered referral for psychosocial treatment as this minimises the likelihood that they will develop significant distress.	I	45
Identification of depression and anxiety is important as these disorders can be effectively treated with a combination of supportive psychotherapy, cognitive and behavioural techniques, and pharmacotherapy.	I	49
• Delirium should be suspected in any patient who demonstrates an abrupt change in behaviour, personality or mood.		
When delirium is suspected, urgent identification and treatment of the cause must take place while pharmacological and non-pharmacological treatments are initiated to reduce the distress of the patient and their family.	IV	46
If organic mental disorder is suspected, the patient must be assessed for treatable causes, and specialist psychiatric advice obtained about management.	IV	46
• The contribution of patient neuropsychiatric symptoms and personality changes to carer distress may outweigh the burden posed by physical symptoms. Patient personality changes can lead to social isolation that compounds distress.		

Key points and recommendations	Level of evidence	Refs
Patients and their families should be informed that in general, talking about their feelings improves adjustment.	II	58
Patients and their carers should be asked about their emotional adjustment and given information about available support groups and specialist services, as these have been demonstrated to be effective in reducing distress.	I	45,66,67
13. Rehabilitation		
Brain tumour patients should receive neuro-rehabilitation and can achieve functional gains and rates of discharge comparable to those of patients with stroke with a shorter hospital stay.	III	5,7
Patients having residual problems after treatment of a glioma, with stable medical status, should be referred to a rehabilitation service with a range of medical, nursing and allied health professionals, for multi-disciplinary assessment and appropriate therapy and support of their problems, involving both the patient and their carers.	III	7-11,18
Physiotherapy should be offered to these glioma patients with residual problems in motor function, strength, and coordination, or balance and gait problems.	III	9,10,20
Occupational therapy should be offered to these glioma patients with residual problems in personal care and independent activities of daily living. As well as treating individual needs, therapy should also address the person's social and physical environment of care, and be supported by social worker intervention.	III	10
Therapy by a speech pathologist should be offered to these glioma patients with residual problems related to swallowing, communication and cognitive function. Where the services are available, this should be supported by assessment and intervention by a clinical psychologist, or a neuropsychologist.	III	7
Glioma patients expecting to return to driving after treatment of their tumour should be referred to a rehabilitation service for full assessment of their ability to drive safely. Any resulting determinations of the driver licensing authority must be observed. For those who can return to driving, regular ongoing follow-up by the rehabilitation service is indicated, to review and manage any on-going risk associated with driving. Those who continue to drive unsafely, contrary to advice and the determinations of the driver licensing authority, should be counselled about the need to behave responsibly and the advice of the authority be sought, if they still continue to drive. In some situations, cancellation of the driver's licence may be necessary.	I	19
14. Follow-up		

Key points and recommendations	Level of evidence	Refs
• The aim of follow-up for patients is to evaluate tumour control, monitor and manage symptoms from tumour and treatment and provide psychological support. • The optimal frequency of follow-up visits is unknown and should be determined by the patient's clinical condition. • Follow-up should be undertaken in a setting where the patient has access to members of the multi-disciplinary team. • Dexamethasone dose should be gradually reduced and ceased when possible.		
15. Palliative care		
Specialist palliative care services can improve outcomes in the care of patients with cancer and should be available for all appropriate patients.	I	6,7,8
• Referral to palliative care should not be limited to the end-of-life phase of illness.		
Methods used to identify survival time have limitations in accuracy and precision and are therefore not routinely recommended for determining the timing of referral to palliative care.	I	21,22
All patients with advanced progressive life-limiting disease should be given the opportunity to discuss prognosis and end-of-life issues.	IV	33
Medications (corticosteroids, megestrol acetate) may be trialled as a treatment of fatigue.	II	40,41
Psychostimulants are not recommended for fatigue, outside of clinical trials.	II	42
Psychosocial interventions and energy conservation may help with fatigue.	II	39
Opioids are the analgesics of choice for moderate to severe cancer pain.	I	44
Artificial nutrition is not recommended in patients with advanced cancer because it does not reduce morbidity or mortality.	I	51
Meticulous attention must be given to mouth care in the dying patient.	IV	53
• The issue of parenteral hydration in the dying patient remains controversial.		
Opioids applied topically (eg morphine paste or liquid) can relieve the pain associated with pressure area wound care.	IV	74

Key points and recommendations	Level of evidence	Refs
• Patients should be maintained on the lowest possible effective steroid dose to minimise side-effects.		
With regard to steroids, the clinician should; • Dose according to each patient's individual needs. • Consider pulsed rather than continuous treatment. • Monitor continuously for side-effects. • If no longer of benefit, wean down slowly and discontinue. • Consider prophylactic nystatin and gastroprotection in all patients, especially those with added risk factors.		
All patients requesting euthanasia should be thoroughly assessed in terms of their symptoms and mental wellbeing, in particular, assessing them for evidence of depression. All symptoms should be managed, including offering treatment and counselling for depression if present.	III	94
• Early and ongoing advanced care planning is important and health practitioners should initiate end of life conversations and advanced care planning as early as appropriate.		
Non-essential medications should be discontinued while essential medications are prescribed by an appropriate route.	IV	95
• Pain is the most common and most feared symptom of advanced disease and analgesics must always be continued.		
Involvement of a community palliative care service makes it more likely that the patient will die at home.	IV	99,100
• Risk factors for complicated grief include: - Male gender - Lack of coping mechanisms - History of mental illness - Multiple losses - Intense brief relationship with deceased - Lack of support and family cohesion - Unexpected or traumatic death - Financial difficulties		
-		

1 SETTING THE SCENE

1.1 Introduction

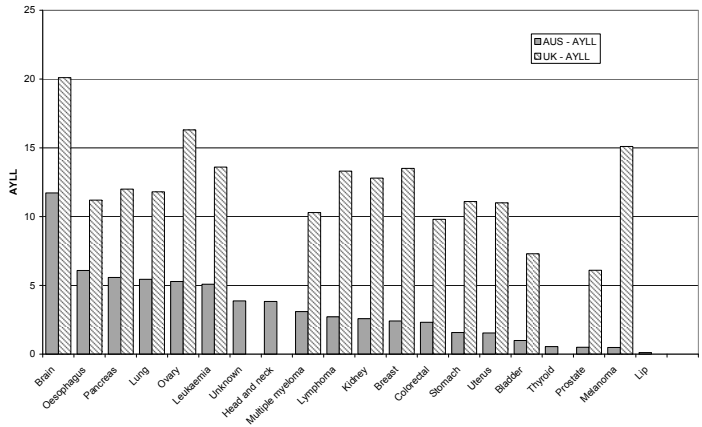
These guidelines cover the most common primary central nervous system (CNS) cancers or malignant tumours known as gliomas, which include astrocytoma, glioblastoma multiforme (GBM) and oligodendroglioma (Table 1.1). The guidelines do not cover secondary (metastatic) cancers that have spread to the brain from primary cancers elsewhere in the body. Nor do they cover benign tumours such as meningiomas, which arise from the membranes surrounding the brain and spinal cord.

Table 1.1 Distribution of astrocytomas and oligodendrogliomas[1]

Tumour type	Percentage of all gliomas
Astrocytoma grade I (pilocytic)	4
Astrocytoma grade II (diffuse)	10
Astrocytoma grade III (anaplastic)	22
Glioblastoma multiforme (grade IV)	52
Oligodendroglioma grade II	3
Oligodendroglioma grade III (anaplastic)	4
Mixed oligoastrocytoma grade II & III	1
Not able to be graded	4

Brain cancers 'are among the most devastating to patients and their carers because they affect the organ that defines the self'.[2] Although these cancers are not common, the average person years of life lost (AYLL) due to primary brain cancers is estimated at 12 years per patient in Australia in 2001.[3] This is much higher than the average for all cancers (three years) because these cancers tend to occur in younger people.[4] The extent of this loss can be seen in Figure 1.1, which shows that the primary brain cancer is associated with the highest AYLL for the common cancers in Australia and the United Kingdom.

Figure 1.1 Average years of life lost for patients in Australia and the UK, 2001, by cancer type



Sources: Burnet et al,[5] Australian Institute of Health and Welfare (AIHW)[6]

Astrocytomas and oligodendrogliomas are the most common gliomas that arise from glial cells. They make up about 40% of all CNS tumours[7] and more than 60% of primary brain cancers.[8] When glial cells were named it was thought that their function was to provide the 'glue' which held neural tissue together, to nourish nerve cells (neurons) and maintain nervous system immunity; recent work suggests that normal glial cells influence synapses and modify neural connections, with implications for learning and memory.[9]

Diffuse astrocytomas occur in any part of the CNS, infiltrate brain structures and can behave in indolent or aggressive ways. They have the tendency to progress from lower (grade II) to higher (grade IV, also called glioblastoma multiforme, GBM) grades of malignancy. However 70–95% of GBM arise *de novo*, that is, without a precursor tumour.[10] Grade I astrocytomas, also known as pilocytic astrocytomas, occur in children and young adults, are less invasive than diffuse astrocytomas and have a relatively good prognosis.

Oligodendrogliomas, which are thought to arise from the cells producing the myelin sheath that insulates nerve fibres, are associated with longer survival than astrocytomas and can respond well to chemotherapy.[11,12] They often present after a long history of seizures and tend to be located towards the surface of the cerebral hemispheres. The number of new cases each year appears to be rising concurrently with a fall in the incidence of astrocytoma[13,14] but this may be due to changing criteria for histopathological diagnosis.

1.2 Incidence

There is a wide variety of CNS tumours, with the World Health Organisation listing more than 120 types.[15] Many of the statistics described in this chapter refer to primary brain cancers, which comprise the bulk of CNS cancers because numbers of other CNS cancers such as cancers of the spinal cord) are too small to report reliably. An estimated 190,000 new cases occur per year worldwide. CNS cancers make up less than 2% of all malignancies.[16] Incidence does not vary greatly between regions or populations.[17] (The global incidence of benign CNS tumours is unknown as most cancer registries do not collect these data.) According to the Australian Institute of Health and Welfare (AIHW), which collects case notifications from all State Central Cancer Registries, in Australia 1369 or 6.8 per

100,000 people were diagnosed with primary brain cancer in 2004, the latest year for which national figures are available.[3] In comparison, approximately 161 new cases of breast cancer and 64 new cases of colon cancer were diagnosed per 100,000 population that year. AIHW ranks CNS cancer as the fourteenth most common cancer in Australia.[18] In the Australian States and Territories, the age-standardised incidence of brain cancer in 2001 (the most recent year for which State data are available) ranged from 6.3 per 100,000 in Western Australia and the Northern Territory to 7.5 per 100,000 in Victoria.[4]

1.3 Changes in incidence over time

Australia-wide, the crude incidence of primary brain and other CNS cancers increased 0.3% per year from 1982 to 2004,[3] similar to increases in some other countries.[19,20] These increases have been attributed to the introduction of computed tomographic scanning (CT) and magnetic resonance imaging (MRI). CT scanning imaged some tumours better after the late 1970s,[21] and after the mid 1980s MRI increased the diagnosis of low-grade astrocytoma which had been less visible using CT scanning.[22] After adjusting for patient age, incidence of brain cancer increased by an average of 0.1% per annum in males and decreased by an average of 0.8% per annum in females between 1991 and 2001.[4] The increased incidence over time was mostly in people over 65 years old, probably because non-invasive CT and MRI has improved diagnosis in older people.[23]

1.4 Influence of age and sex

Primary brain cancer is most commonly diagnosed in childhood and in adults 45–70 years of age, of both sexes. In children, brain cancers are the most common malignancy after leukaemia. Posterior fossa tumours predominate in children, but cerebral hemisphere tumours predominate in adults. The median age at diagnosis of brain cancers in Australia was 55–59 years for males and 60–64 for females in 1999.[23,24]

Incidence rates are higher in males for primary CNS cancers (1.3:1), whereas females have a greater incidence of meningiomas (around 1.5:1).[25]

1.5 Influence of socio-economic status and geographic area

Australian studies have shown that survival of patients with cancers other than glioma varies according to socio-economic strata (SES) and geographic differences.[26–29] A recent report shows that these factors also independently affect survival of patients with glioma in England and Wales[30], and suggests that chronic co-morbidities and differences in effectiveness of healthcare systems may be responsible for these inequalities. There are no Australian data comparing survival of glioma patients by SES or geographic location, but New South Wales data show no significant variation in survival between Area Health Services.[31]

1.6 Mortality

The death rate from brain cancer is higher in developed countries than in the less-developed countries, probably because of better detection of cases rather than worse treatment in the more developed countries. Brain cancers rank 12th in order of cancer-related deaths in most developed countries[16] and 10th in Australia.[4] In Australia 1048 people died from brain cancer, that is, 2.9% of deaths from malignancy, in 2004.[3] Mortality fell by an average of 1.2% per year between 1994 and 2004 to 5.4 deaths per 100,000 in 2004.[3] The median age at death was 60 years, the youngest age of the 14 cancer types for which these data were reported.[4]

1.7 Survival

According to the AIHW, 24% of Australians diagnosed with all brain cancers between 1992 and 1997 survived for five years.[6] There was no increase in survival in Australia over the periods 1982–1986, 1987–1991 and 1992–1997.[6] Relative survival of all patients diagnosed with brain cancer between 1997 and 2004 was 20% at five years and 16% at ten years.[32]

Younger age, good preoperative performance status and gross macroscopic resection have been associated with longer survival in patients with astrocytoma and oligodendroglioma.[33] After resection, average survival for grade II astrocytomas reported internationally is around five to eight years,[34,35] for grade III (anaplastic astrocytoma) about three years [36] and for grade IV (GBM) less than one year.[37] A recent Australian study reported all grades of Victorian glioma patients to have a median survival of 9.2 (range 0–84+) months and GBM patients to have a median survival of 7.4 (range 0–84) months.[38] A long-term study of astrocytoma patients between 1980 and 2004 in Northern Sydney reported median survivals of 64 months for grade II, 11 months for grade III and eight months for GBM.[39] These figures relate to patients treated before 2002 when treatment with concurrent radiotherapy and chemotherapy was introduced[40] (see *Chapter 8 High-grade astrocytomas*).

Reported survival times for oligodendrogliomas vary widely because of the low incidence of these tumours, difficulties classifying them and various genetic subtypes.[41] Low-grade oligodendrogliomas are reported to have median survival times of up to ten years, while for anaplastic oligodendrogliomas (grade III) median survival times range between one and seven years.[42]

1.8 Predisposing factors and causes

Many possible risk factors including diet, occupations, alcohol, tobacco, drugs and a history of infection or trauma have been explored for evidence of a causal link with brain cancers, but the associations seen are weak and inconsistent. Known predisposing factors for astrocytomas and oligodendrogliomas include increased age, male sex and a rare familial (inherited) tendency. Rare familial syndromes involving the nervous system include neurofibromatosis types 1 and 2, Li-Fraumeni and Turcot. Patients with these syndromes are at increased risk of developing gliomas.[43]

Ionising radiation[44,45] has been convincingly recognised as a cause of brain tumours, but such cases are rare[46]. For most patients no cause has been clearly identified—the vast majority of brain cancers appear to arise randomly. Non-ionising radiation has been suspected as a cause of brain cancers for many years, but studies in electrical workers and mobile phone users have shown either no effect or a slight increase in incidence of benign brain tumours associated with prolonged use of old-style analogue phones. Even those studies most recently available do not agree on evidence of an effect.[47,48] Any radiation exposure from a mobile phone to the brain will be less than to the ear, because of the inverse square law: as the distance from an energy source doubles, its effect is reduced to a quarter.[49]

1.9 Why we don't know what causes primary brain cancer

There are three main reasons it has been difficult to determine the causes of astrocytomas and oligodendrogliomas:

- the heterogeneity of these tumours and an historical lack of specificity of diagnosis
- small numbers of specific tumour subtypes
- the use of retrospective study designs, particularly case-control studies.

Historically, epidemiological studies have classified all CNS cancers together because there was little detail of the histopathological diagnosis available from cancer registries, which are the main source of population-based ascertainment for research subjects. Mixing all CNS cancers together as if they all share the same causal risk factors will diminish the chance of detecting any association that might be specific to one tumour type. This problem is beginning to be addressed by recent studies that restrict

case ascertainment to glioma as a group. Much still needs to be done and it is hoped that our increasing understanding of the molecular biology and genetics of gliomas may help define subtypes with precision.

Even the most frequently diagnosed morphological subtypes of these tumours are not common, and most can be considered rare. It is extremely difficult, therefore, to study sufficient numbers of cases from which to draw statistically significant conclusions. The rapid fatality of many of these tumours also biases studies towards those subjects that survive long enough to be interviewed.

Because of their rarity, the usual approach to researching the epidemiology of brain cancers has been to conduct a case-control study, which is an observational study in which the occurrence of an attribute in people with the disease (or other outcome) of interest in a population is compared with the occurrence of the same attribute in the same population at large. Those with the disease or (or other outcome) of interest are called *cases*. The occurrence of the attribute in the population at large is determined in a sample of the population known as the *control* group. The design of case-control studies varies with respect to the selection of cases and controls. The problems with this approach are many, but for brain cancers in particular there is the possibility of the cancer and/or its treatment directly affecting the ability of the subject to recall past events. In this situation, the differences in information obtained from cases and controls can cause bias in estimating risks that may lead to spurious findings.

Given the large number of ongoing prospective studies internationally, plans are being made to pool glioma cases for analysis thus avoiding the problem of recall bias. Research into genetic mechanisms involved in brain tumour biology is very active. Future gains in our understanding of the molecular pathology of gliomas could assist the search for causes by increasing our ability to classify gliomas in a more biologically meaningful way.

1.10 Prevention

Because no causes have been convincingly identified for astrocytomas and oligodendrogliomas, no specific preventive measures can be recommended.

1.11 Screening

Screening is most effective for cancers that occur commonly; where there is a cheap, specific and safe test that detects the tumour at an early stage; and where an effective treatment exists that works best when the tumour is found in an early stage. Although screening is available for cervical, breast and bowel cancer in Australia, there is no known cost-effective way to screen for brain cancers because they are rare and early detection does not greatly increase the benefit of treatment. An exception is the potential use of genetic testing to identify patients with neurofibromatosis type 1, who are at risk of developing optic glioma, a slow-growing tumour which can impair vision.[50]

Key points:

- Astrocytomas and oligodendrogliomas comprise the largest proportion of primary CNS cancers.
- Primary CNS cancers are diagnosed in 7/100,000 Australians each year, compared with colon cancer 60/100,000/year.
- Although uncommon, CNS cancers are associated with the highest person years of life lost (PYLL) of all major cancers—on average 12 years per patient.
- Astrocytomas and oligodendrogliomas have a tendency to progress to higher grades of malignancy over time.
- Gliomas are more common in males. Median age at diagnosis is 55–59 years in males, 60–64 years in females.
- Incidence has increased slightly over the past twenty years, probably due to increased life span, improved imaging and more investigation in elderly patients.
- Incidence of glioma does not vary much between geographical areas.
- Median survival after resection is 5–8 years for low-grade astrocytoma, three years for patients with anaplastic astrocytoma, about one year for patients with GBM, up to ten years for low-grade oligodendroglioma and 1–7 years for anaplastic oligodendroglioma. Younger age, good preoperative performance status and gross macroscopic resection are associated with longer survival.
- Nearly all CNS cancers arise randomly. The only known cause is ionising radiation.
- Known risk factors for developing glioma are increased age, male sex and rare familial genetic syndromes.
- Except possibly for neurofibromatosis type 1, no screening test is available for glioma as early detection does not increase the benefit of treatment.

1.12 Some useful links

1. Independent Expert Group on Mobile Phones. Report of the Group (The Stewart Report): http://www.iegmp.org.uk/documents/iegmp_5.pdf
2. Australian Radiation Protection and Nuclear Safety Agency has information about mobile phones and electromagnetic radiation: http://www.arpansa.gov.au/mph1.htm
3. The Cancer Council of Australia has general information about cancer, including dietary advice. http://www.cancer.org.au/
4. NSW Cancer Institute Incidence and Mortality Report 2004: http://www.cancerinstitute.org.au/cancer_inst/publications/pdfs/IncidenceMortalityReport2004.pdf

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2 APPROACH TO THE PATIENT

2.1 Issues facing patients

A diagnosis of a brain tumour can result in a broad range of complex physical, cognitive and psychological symptoms. The ensuing functional impairment, loss of independence and potentially severe disabilities are distressing for patients, their families and care givers. These issues are expanded in *Chapter 12 Psychosocial care*.

There are specific challenges that arise when a patient is diagnosed with a brain tumour that are not as commonly encountered in the management of other solid tumours.

Specific symptoms commonly experienced by patients as a direct result of brain tumours include problems with memory (affecting comprehension and compliance), impaired judgement, and personality changes. These are often compounded by limited insight. In addition, poor mobility, weakness, speech impairments (such as aphasia), impaired vision, and seizures pose considerable difficulties.

Health professionals involved in the care of patients with brain tumours must also be aware of the potential toxicities of treatments. For example, treatment with steroids may be associated with emotional lability, insomnia or reversal of sleep–wake cycle, high blood sugars (or exacerbation of existing diabetes), and steroid myopathy exacerbating mobility problems. Similarly, anticonvulsants, oral chemotherapy, antiemetics, aperients, prophylactic antibiotics and anticoagulants may cause side-effects and interact with medications for co-morbid conditions.

2.2 Issues facing carers

Family members and carers of patients with brain tumours face a number of unique challenges. Carers often assume a major responsibility in coordination of the patient's care, which may involve extensive travel for specialist treatment and in cases of the patient's cognitive impairment, the carer may have a central role in communication with health professionals and in decision-making. It is important not to overlook the effect of practical adjustments that have to be made, for example, modifications to housing to allow for wheelchair access. Especially for younger patients with a mortgage and dependent children, the inability to work may pose significant financial hardship, which is exacerbated if their partner is unable to work because of caring responsibilities. It is important that clinicians ensure all carers have access to a person (such as a social worker) who has a clear understanding of the available services–health, financial (eg availability of carer's pension, and early access to superannuation) and social–that may be appropriate for individual patients.

Key point:

- The approach to the patient must include recognition of the concerns of family members and caregivers and incorporate attention to complex medical and psychosocial issues.

2.2.1 Access to treatment

The care pathway for patients may be complex because of the number of health professionals involved, and the potential for geographical separation of neurosurgical, chemotherapy and radiotherapy treatment centres for a large proportion of those diagnosed. The period from initial presentation of symptoms to diagnosis and subsequent treatment all add significantly to individual and collective stresses and anxiety experienced by the patient and family.[1]

Following initial treatment many patients may experience a lengthy period of both physical and cognitive deterioration, often without referrals to timely and appropriate support services.

Assessment and management of complex cognitive, emotional, personality and behavioural problems from specialist psycho-oncologists, neuropsychologists and/or neuropsychiatrists should be offered if readily available. Assessment should occur on a continuing basis, including monitoring of any cognitive and personality changes according to disease progression.

2.2.2 Multidisciplinary approach

There are no prospective trials that have examined the role and effectiveness of multidisciplinary teams in the field of neuro-oncology. A retrospective comparison of two hospitals with and without multidisciplinary care (MDC) demonstrated better clinical quality outcomes for brain tumour patients managed by MDC. MDC patients were more likely to receive post-operative imaging and early radiotherapy and had improved median survival.[2] The model of multidisciplinary care is well established in many areas, for example, the care of breast cancer patients (NBOCC).[3] Expert opinion states that the optimal care of all patients with a brain tumour should be delivered and coordinated by a multidisciplinary team. The team members can include: neurosurgeon, radiation oncologist, medical oncologist, neurologist, endocrinologist, rehabilitation physician, palliative care physician, clinical care coordinator, social worker, occupational therapist, physiotherapist, community nurse, inpatient team (registrars, nurses, etc), dietician and others. Brain tumour care coordinators and brain nurse practitioners are not widely available in Australia, but would be desirable in most settings. Involvement of community and palliative care services may be required soon after diagnosis for patients with high-grade tumours. The social worker is also an integral part of the team and will coordinate financial and emotional support. The patient may need a disability allowance, a carer's allowance, access to superannuation or a variety of other services. The general practitioner (GP) should also be regarded as an integral part of the team and may provide the long-term continuity of care.

Timely communication between health-care professionals is particularly important for patients with brain tumours whose care pathway is often complex. All team members need appropriate accurate knowledge and understanding of the patient's current situation so they can facilitate involvement of family and caregivers in management and decision-making and so that clear consistent information is given to patient, family and caregivers. Members of the team need to be aware of any aspects of the individual's and family's culture, religious beliefs or social background that may affect their response to information.

Good team communication may 'maximise the technical synergy of care'.[4] Information should be forwarded to the patient's GP and other treating clinicians as soon as practicable after consultations, including relevant details regarding diagnosis, clinical findings, future tests/test results, treatment recommendations, likely side-effects and prognosis[5] and the response of the patient and family to the information given.

2.2.3 Coordination of care

A patient may be treated by many different health professionals during the course of their illness, and effective coordination of care may improve the outcome. Continuity of care is considered important; frequent staff changes are disruptive and counter-productive, both for the patient and from the professional point of view.

To help maintain continuity of care, it is suggested there be a designated lead clinician who may change with time and who bears overall responsibility for the relationship with the patient. The choice of the person to coordinate care should be made by the patient in conjunction with their general practitioner and other specialists.[6,7]

2.3 Specific communication issues: information provision

There are different challenges at different junctures of the disease journey.

2.3.1 Diagnosis

Initial consultation

It is essential that the patient and their support person(s) be informed from initial presentation that an accurate diagnosis can only be obtained when the test results are reviewed by the treatment team. Frozen sections should not be relied upon for diagnosis. Frozen section is only a technical aid during resection. Tissue confirmation of diagnosis may not be available for up to a week (occasionally longer) after the surgical procedure due to the need for special histopathological stains and possibly specialist neuropathology review. Some molecular or genetic testing will take longer than a week.

Studies have shown that only a proportion of the information given in the initial consultation is remembered[8] hence it is important to check understanding, repeat information and provide communication aids such as CDs, DVDs, audiotapes or personalised letters from the consultation, although they may not increase knowledge or recall.[9,10] Educational resources should be readily available and provide clear accurate and relevant information about each malignant tumour type and explanations of commonly used terms and patterns of care. Involving consumers in developing patient information materials can improve the clarity and relevance of materials, and can improve people's knowledge without increasing their anxiety about medical procedures.[11] Details should be provided about local and national societies, appropriate websites and other relevant publications including self-help and support in their area, particularly voluntary organisations that have relevant helpline and information services.

At each stage of the patient care pathway, information on any relevant clinical trials, research on a particular treatment and palliative care services should all be available for patients, their families and caregivers.

Interpreter services should be used when lack of English proficiency may inhibit communication between the patient and their health-care provider. Furthermore, it may be appropriate to seek the assistance of some culturally and linguistically diverse professionals (eg Aboriginal and Torres Strait Islander) in circumstances where cultural differences inhibit effective communication. The interpreter should be a professional and not a family member.

Breaking bad news

Breaking bad news in language the patient understands is usually the responsibility of the lead clinician who knows the patient and is likely to be actively involved in the ongoing management plan.[12] Evidence suggests that most cancer patients wish to be fully informed of all available information and they usually want a close relative or friend present at the initial consultation.[13] Patients report that the subsequent discussions about treatment plans and what the diagnosis means are at least as important, if not more important than, the disclosure of the initial diagnosis.[14]

It can be very confronting to a clinician when a family, with good intentions, wishes to protect the patient from disclosure of their diagnosis or from the decision-making process. However, the primary responsibility of the clinician is to the individual patient. Where culturally appropriate, the patient should ideally be asked about their preferences for the provision of information.

There will be several occasions during the care of an individual with a glioma that bad news needs to be delivered.

These points in time can include:

- initial diagnosis
- at time(s) of disease progression

- at the time no more active treatment will be offered (due to poor performance status or not having further options available)
- at a time when the family do not feel they can continue to care for the patient at home.

Recommended steps for breaking bad news
Prior to discussing the diagnosis • Ensure the news is given in person in a quiet private place and allow enough uninterrupted time. • Encourage a second person to be present if appropriate. In the presence of cognitive impairment this is essential. • Arrange to provide other methods to convey information such as written material, DVDs, videotapes, etc.
When providing the information • Assess the person's understanding of their condition and their personal preferences for information. • Briefly explain the process by which the diagnosis was reached. • Provide information simply and honestly, using lay terms without euphemisms. • Avoid giving the message that 'nothing can be done'. • Clearly indicate that the patient will have the final decision regarding their care.
Emotional and supportive role • Encourage the person to express their feelings and talk about fears or concerns, and respond with empathy. • Address disturbing or embarrassing topics directly, with sensitivity. • Assess the type and level of assistance that may be required, such as financial assistance or transport services. • Provide information about support services.
Concluding the discussion • Summarise the main points of the consultation and check the person understands. • Ask if there is anything further the individual would like to discuss. • Offer assistance to tell others the difficult news. • Indicate your availability for contact to address questions or concerns.
After discussing diagnosis or recurrence • Document information given to the person and family members. • Let others, especially the person's general practitioner, know the extent of the information given and your perception of the person's understanding.
Adapted from *Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer 2003*.[7] Reproduced with permission

Families, partners and children

It is appropriate for clinicians who break the news of the diagnosis to the patient to ask about the family's and children's adjustment, clarify what assistance may be required in discussing diagnosis and treatment with family and children, and facilitate referral for information and support as needed.

When a patient clinically does better than expected, this can pose certain unexpected challenges such as the need for discussion about ongoing treatment (and limitations of treatment) and issues such as carer fatigue or 'burn-out'.

For patients with young children the resource produced by The Cancer Council of New South Wales: *When a parent has cancer: how to talk to your kids. A guide for parents with cancer, their families and friends* 2005[15] should be provided to the patient and the partner/carer.

2.3.2 Discussing prognosis

Gliomas are generally incurable. High-grade gliomas generally have a short prognosis (years to a few months depending on whether grade III anaplastic astrocytoma or IV glioblastoma). The prognosis of a low-grade tumour can be difficult to predict as it is difficult to know which patients have tumours that will transform into higher-grade tumours and it is also difficult to predict when such a transformation will take place. The discussion will be different according to whether one is discussing prognosis with a patient with a low-grade glioma (longer prognosis usually) or a patient with a high-grade glioma (who will have shorter prognoses on average). More detail on prognosis is provided in *Chapter 1 Setting the Scene* and in *Chapters 7 Low-grade astrocytomas*, *8 High-grade astrocytomas* and *9 Oligodendrogliomas*.

Most patients want to receive prognostic information because it helps in their decision-making.[16-18,19-21] Key points to consider in discussing prognosis include:

Timing

It is important at the time of diagnosis (once the pathology results have been reviewed) to have a discussion relating to prognosis that is tailored to the patient's (and carer's) needs.

Tailoring to the individual

Some people desire as much information as possible; others prefer minimal information. A patient's need for information may alter over time as the treatment proceeds and symptoms fluctuate. The safest option it to check the patient's preferences for information and review this over time. Information will need to be tailored to aid understanding if the patient has cognitive impairment. Relatives often give a guide to the patient's tolerance for information and the family's wishes should be considered as well as the cultural context. However, the patient's autonomy and rights are paramount.

Language

Information should be given honestly in simple language without use of jargon. Vagueness and obscurity make a difficult situation worse.[22] It is useful to give average and longest survival times, emphasising a range rather than a single time point, and to present information in a variety of formats, for example words, statistics or graphs.[18]

Maintaining hope

Most patients prefer that their clinicians speak plainly and in clear language. A study of patients with advanced cancer found that 82% of patients did not consider that the use of euphemisms by their doctor would promote their hope.[23] In this study, physician behaviours found to be more likely to promote hope included treating the person as an individual, being realistic about the likely future,

placing emphasis on what can be done rather than what can't be done, and checking how the person is feeling.

Emotional support

It is extremely important that patients are allowed to express their feelings and that these expressions receive an empathetic response.

Consensus guidelines provide supporting evidence and practical strategies to assist health professionals in discussing prognosis.[17,18,24]

Discussing treatment options

The National Health and Medical Research Council (NHMRC) *General guidelines for medical practitioners on providing information to patients*[25] state that patients are entitled to make their own decisions about treatments or procedures and should be given adequate information on which to base those decisions:

- *Information should be provided in a form and manner which helps patients understand the problem and treatment options available, and that is appropriate to the patient's circumstances, personality, expectations, fears, beliefs, values and cultural background*
- *Doctors should give advice, but should not coerce*
- *Patients should be encouraged to make their own decisions*
- *Patients should be frank and honest in giving information about their health, and doctors should encourage them to do so*

The medico–legal aspects of competency are covered in *Chapter 12 Psychosocial care*. The medico–legal aspects regarding ability to consent to participate in a clinical trial are in *Chapter 3 Clinical trials and research*.

Decision-making

There has been a trend for patients in all health settings, including oncology, to be increasingly involved in decisions regarding their treatment.[26] However decision-making is often complex, and on occasions the risks and benefits of particular treatments may be difficult to predict.[27,28] For some patients, involvement in decision-making is unfamiliar[29] and they may find decision-making more difficult because of the stress surrounding diagnosis.

It is important that any discussion between doctor and patient should attempt to establish the patient's values and preferences for involvement in decision-making. For shared decision-making to be achieved, patients need to understand the information presented, ask questions to clarify outstanding issues, weigh up the available treatment options and state their preferred option. In a shared decision-making model, the patient and oncologist make the final treatment decision together, having considered the patient's values, the risks and benefits of alternative treatment options and through a process of negotiation.[30,31]

While shared decision-making is generally considered to be optimal, there may be particular barriers to shared decision-making in neuro-oncology. Doctors must be able to translate the scientific findings of research into lay language that is relevant to the particular patient's situation[32], however if the patient has cognitive impairment this is complex to do. There is evidence that many patients find it difficult to define their preferences for information and involvement in decision-making, however cognitive impairment is common for patients with brain tumours[33] and this may impede their ability to communicate their own values and preferences. In the most extreme instances, patients' level of cognitive compromise can render them incapable of making decisions. However, it remains important

to ensure that patients are as involved in the decision-making process as they are cognitively able to be. A number of measurement tools exist to facilitate accurate assessment of patients' competence. Taphoorn and Klein[34] recommend the use of a comprehensive series of tests which cover the different cognitive domains including memory, attention, orientation, language abilities and executive function.

Given the poor prognosis and significant potential for cognitive impairment, it is particularly important in neuro-oncology to pre-empt difficulties which might arise in relation to the decision-making capacity of these patients. While some patients have considered in advance the nature of treatments that they would want should they become incapable of making a decision, such orders are often poorly understood and not extensively exercised[35,36] so it is important for their neurosurgeon or oncologist to ask about any existing advanced directives and to clarify any ambiguous points. The ideal approach is for the oncologist to introduce the subject of decision-making and assist the patient in expressing their wishes while competent to do so, rather than reacting only when faced with the patient's incapability. Additionally, it is helpful to have the patient nominate a surrogate decision-maker (usually a close family member) who could make decisions on the patient's behalf should the patient become incapacitated and who is aware of the patient's wishes. Ideally, this person would be involved in medical discussions with the patient and the doctor as early as possible in the illness trajectory. If a patient nominates a person to make treatment decisions on their behalf, this is considered a suitable alternative to informed consent.

Although many clinicians may feel that discussing these issues is confronting, in fact most patients feel relieved to be able to express their concerns, and less distressed that they are placing a burden of responsibility on family members. After open discussion, family members often feel more confident that they will be able to 'do the right thing' to respect the values and wishes of the patient, rather than struggling with doubt and guilt, which is common if the patient has not expressed their views.

If the patient is incapable, a number of options are available to oncologists to determine the appropriate medical management. These options vary between jurisdictions and are described in detail in *Chapter 12 Psychosocial care*.

Key point:

- Cognitive deficits are common with gliomas and can impair patients' abilities to comprehend information and specifically their capacity to provide informed consent for treatment. In the area of shared decision-making, the guiding principles should be to respect patients' autonomy and to act in patients' best interests.

While conflict that cannot be resolved through a process of shared decision-making with the patient or their surrogate is likely to be rare, given the nature of glioma these situations may arise more often than in many areas of medicine.

Good practice points:

- Present information in a clear and unambiguous way. Avoid medical jargon and use lay terms where possible.
- Encourage the patient to ask questions about any aspects of the treatment/s.
- Elicit the patient's values and preferences.
- Negotiate a treatment decision with the patient.
- Where possible, include another person in the room during your consultation with the patient (essential if there is any degree of cognitive impairment).
- Where possible, aim to discuss while the patient is still competent to make decisions the sort of treatment and care they would like to receive if their illness progresses.
- Ask the patient to nominate a surrogate decision-maker should their condition deteriorate and encourage the patient to discuss their wishes about treatment with this person.

2.4 Other aspects of approach to the patient

2.4.1 Second professional opinion

Patients have the right to obtain a second opinion at any time. A second opinion may help patients to clarify questions and to decide which doctor they prefer to manage their condition and which course of treatment to follow. It can also reinforce the accuracy of advice already given, and enhance the patient's confidence. Doctors should cooperate fully in providing both a referral and all relevant information.[37]

2.4.2 Preparing patients for potentially threatening procedures and treatment

People diagnosed with a brain tumour may undergo a number of traumatic medical procedures and interventions, such as surgery, biopsies, radiotherapy and chemotherapy. Provision of procedural information about the treatment plan significantly reduces emotional distress and anticipatory side-effects, and improves psychological and physical recovery.[38,39] Examples of procedural information include discussion of practical issues such as where the procedure will take place, what it involves, for example the noise associated with an MRI, how long it will last, etc. This information can be provided by a clinician or allied health professional[40], booklets[41], video information[42], models or images. The addition of sensory information can further reduce anxiety.[34] Sensory information refers to what the person is likely to experience and feel during the procedure, such as discomfort or pain, including possible emotional responses.

2.4.3 Supportive care

Supportive care is an encompassing term for the services provision from a wide range of health-care professionals to address the changing needs of patients, families and caregivers throughout the patient journey. The way a clinician and treatment team relates to and communicates with a patient can significantly benefit the patient and their family.[43] Encouraging patients to talk about their concerns is important, as there is evidence that this reduces patient distress.[44] Specific strategies for provision of support are described in more detail in *Chapters 12 Psychosocial care* and *13 Rehabilitation*. In addition, there is clear evidence that training in communication skills improves the ability of health professionals to respond to the emotional concerns of patients.[45]

2.5 Other challenging communication issues

There are many other communication challenges for the health professionals caring for a patient with a brain tumour.

For example, many patients do not cope well with the discussion around no longer being able to drive if they have active tumour (see *Chapter 13 Rehabilitation*). Other challenging communication issues may include placement issues (eg whether a patient can be managed at home versus care in a nursing home, which can cause arguments within families) or the discussion of advanced directives (see *Chapter 15 Palliative Care*).

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3 CLINICAL TRIALS AND RESEARCH

3.1 Background

A clinical trial is a study 'that involves the administration of a test regimen to humans to evaluate its efficacy and safety. The term is subject to wide variation in usage, from the first use in humans without any control treatment to a rigorously designed and executed experiment involving test and control treatments and randomisation'.[1] Clinical trials are the foundation of most improvements in cancer therapies, including treatment of brain tumours. Clinical trials are usually the result of years of scientific investigation in the laboratory and in animal models. Treatments that appear promising must then be tested in clinical trials on patients to determine how the treatment should be given, the safety and side effects of the treatment, and how effective it is in people with a given condition.

3.1.1 Phase I, II, and III clinical trials

Clinical drug trials take place at different stages in the development of a potentially useful treatment. Phase I, II and III trials have different designs and may be suitable for different patient populations.

Phase I trials are the first studies in patients that are done to find out how the drug should be given, how often, and what dose is safe. Few phase I studies are done in Australia in patients with gliomas. Small numbers of patients are required for most phase I studies, which are usually done in a single centre.

Phase II trials continue to test the safety and toxicity of a drug or combination but also begin to evaluate how well the drug works in the disease and setting of interest. Phase II studies usually focus on a particular type of cancer, and in general all patients receive the same treatment under evaluation.

Phase III trials test a new drug, combination, or surgical or radiation treatment against an accepted standard treatment. These studies can tell us how a new treatment compares with a standard treatment in terms of efficacy, safety and side effects. Phase III trials are randomised, in other words, neither the patient nor the doctor can choose which treatment the patient receives. This is to ensure that the patients in all treatment groups are similar to each other. Phase III trials in cancer are usually not blinded, in other words, both the patient and the doctor know which treatment the patient is receiving. This is usually because it is difficult to blind treatments that are given in very different forms or schedules, and have different side-effect profiles. Sometimes there is no accepted standard treatment for the cancer, and patients are randomly allocated to the new treatment in comparison with 'best supportive care' or placebo.

Phase IV trials are usually trials run after a new treatment is proven to be effective and approved for use. Such trials may allow patients to access a new treatment that is not widely available due to cost or one that is not available on the Pharmaceutical Benefits Scheme (PBS). Such trials collect further information about safety and rare toxicities of new drugs and allow clinicians to become familiar with the use of a new treatment in a controlled situation.

3.1.2 Why clinical trials are important

Clinical trials are important because only proper, rigorous scientific testing can establish whether a new treatment is better than the best available standards. Recent advances in brain tumour treatments have been made after analysis of large and well-conducted clinical trials, including the recommendation to use combined radiotherapy and chemotherapy and adjuvant chemotherapy with temozolomide in initial treatment of patients with glioblastoma multiforme[2] and the demonstration that surgery with implantation of carmustine (BCNU) impregnated wafers is superior to surgery alone in treatment of glioblastoma multiforme.[3] Such trials have led to Therapeutic Goods Administration (TGA) approval and Pharmaceutical Benefits Scheme (PBS) listing of new treatments for brain tumours in Australia. Areas where randomised clinical trials have never been done remain open to

controversy, for example, there is no unequivocal evidence that gross total resection of high-grade gliomas is better than partial tumour debulking or biopsy alone.

3.1.3 Conduct of clinical trials in patients with brain tumours

In Australia, clinical trials in patients with brain tumours may be conducted by several mechanisms.

- *Pharmaceutical companies*. Pharmaceutical companies that develop new drugs must complete phase I, II and III trials before they can market their product. Many clinical trials of new treatments for brain tumours are sponsored by pharmaceutical companies. A prominent expert in the area is often chosen to be the Principal Investigator and is involved in developing the trial protocol. Participating clinicians may also contribute to protocol development. Such trials usually have a sound scientific rationale and are well designed and rigorously conducted.

- *Cooperative groups*. Cooperative groups are groups of clinicians and researchers interested in specific diseases. Cooperative oncology groups in Australia with a special interest in brain tumours include the Trans Tasman Radiation Oncology Group (TROG) and the Cooperative Trials Group for Neuro-Oncology (COGNO). These groups may obtain funding from competitive Federal or State grants to run a trial to answer an important clinical question. Pharmaceutical companies sometimes provide financial support or drugs for such trials. Most cooperative group trials are investigator-initiated, that is they are conceived and initiated by specialist doctors at one or more institutions.

- *Single institutions and consortia*. Some investigator-initiated studies are done at a few hospitals or units.

3.1.4 Ethical review and governance of clinical trials in brain tumours

Before patients can be enrolled onto a clinical trial in Australia, the trial must be reviewed by other expert clinicians and researchers to ensure that it is scientifically well designed and will be able to answer the study question. It will also have been reviewed by at least one Human Research Ethics Committee (HREC) to ensure that the trial protocol adheres to guidelines for clinical trial conduct as laid out in the NHMRC *National Statement on Ethical Conduct in Human Research* (2007).[4] The HREC is also required to evaluate the scientific merit as part of the ethical review unless it has already been done elsewhere and it should ensure that no member of the trial team has an undisclosed conflict of interest.

3.1.5 Patient participation in clinical trials for brain tumours in Australia

In a recent review of 828 patients from the Victorian Cancer Registry with gliomas, 39 patients (5%) were enrolled on a clinical trial during their illness.[5] The National Cancer Research Network in the United Kingdom set a target in 2000 of doubling participation in clinical trials for all cancer patients, and reached that target in 2004, with 10.9% of all patients being enrolled in a clinical trial.[6] However, this remains a small proportion of all cancer patients. There are no specific guidelines for clinical trial enrolment targets for patients with brain tumours in Australia or elsewhere. However, ideally, all patients should have access to treatment in a centre where clinical trials are offered. It is recognised that in Australia the distance of some patients from a tertiary referral centre will be a barrier to access and participation in clinical trials. Elderly patients are under-represented in clinical trials, and patients who are otherwise eligible should not be excluded solely on the basis of advanced age. Enrolment in studies of less common brain tumours such as anaplastic astrocytomas and oligodendrogliomas should be encouraged but it may be necessary to collaborate internationally to accrue sufficient numbers for a meaningful study.

3.1.6 Special issues surrounding clinical trials for brain tumour patients

The requirement for obtaining informed consent is a core principle of clinical trial participation. This requirement is more difficult when patients suffer cognitive impairment, impairment of judgment, and receptive dysphasia. Nevertheless, the National Statement states that people with cognitive impairment are entitled to participate in research.[4]

The National Statement[4] provides guidance for recruiting patients with a cognitive impairment that includes consent being given by a person with lawful authority to decide for that participant (*see Chapter 2 Approach to the patient*; *Chapter 12 Psychosocial Care.)* It is important to note that the law, and therefore the mechanism, by which a person may perform the role of 'guardian' for the person unable to give consent differs in each Australian jurisdiction. For this reason it is important to become familiar with the local and Federal legislative regulations and establish whether a person has authority to give a lawful consent on behalf of another. In some jurisdictions (for example, Western Australia) the law does not include consent being given for participation in research, only for treatments that may be in the best interest of the patient. In certain circumstances then the physician's judgment that enrolment in a trial is consistent with treatment likely to be in the patient's best interests may be sufficient justification for lawful enrolment. In these instances the senior next of kin or person responsible should be identified and informed of the decision and the reasons for it.

A minority of patients may have a physical disability that renders them unable to sign a consent form despite intact cognition (eg dominant hemisphere involvement and hemiparesis). Such patients should not be excluded from clinical trials if they are otherwise eligible. Alternatives may include verbal consent witnessed by an independent third party, or an individual authorised under relevant Guardianship legislation may sign the consent form.

3.1.7 Design of valid and meaningful clinical trials in brain tumours in Australia

Investigators should pay attention to general principles of clinical trial design and reporting such as those set out in the Consolidated Standards of Reporting Trials (CONSORT) statement.[7] However, some important points are more specific to clinical trials in brain tumours.

3.1.8 Recommended stratification variables for brain tumour trials

Stratification for known important prognostic factors should be used:[8,9]

- age
- Karnofsky or ECOG performance status
- biopsy only versus gross total resection or debulking
- histology

Factors may be grouped using recursive partitioning analysis to identify distinct prognostic groups.[10] In addition, genetic markers of prognosis (eg 1p19q loss of heterozygosity) are becoming more important and stratification for these variables should be considered.[11]

Central pathological review

Central pathology review by a specialist neuro-pathologist should be performed whenever possible in clinical trials in brain tumours. Identification of oligodendroglial components is particularly important in view of the increased sensitivity of these components to chemotherapy[12] (*see Chapter 9 Oligodendroglioma*). Inter-observer variability is particularly marked for intermediate-grade tumours such as anaplastic astrocytomas, with concordance rates as low as 36% in some series.[13] Confirmation of tumour grade is particularly important where survival or progression are endpoints.[14]

Central radiological review

Central radiological review by a specialist neuro-radiologist should be performed wherever possible in clinical trials with glial tumours due to the high degree of inter-observer variability in assessment of response.[15]

Ideal trial management committee structure

Trial design should be overseen by expert clinical trialists. A multidisciplinary trial management committee is recommended for all brain tumour clinical trials. Suggested participants include:

- neurosurgeon
- radiation oncologist
- medical oncologist
- biostatistician
- neuroradiologist
- consumer
- consider nurse researcher
- consider health-related quality of life (HRQL) researcher
- consider neurocognitive function researcher
- consider neuropathologist

A quality assurance committee should be established to monitor adherence to the trial protocol so that treatments are standardised between centres.

3.1.9 Recommended study endpoints for brain tumour clinical trials

Overall survival

Overall survival is the most reliable and preferred endpoint for phase III studies in many tumour types. However, there is some concern that overall survival may not always reflect patient benefit in neuro-oncology, with functional and cognitive status being particularly important due to their frequent impairment in this population.[16]

Time to progression

Time to progression (TTP) must be defined strictly in the clinical trial protocol, as there is no standard definition. This endpoint usually reflects the time from enrolment until progression as defined on imaging criteria (which may be study-specific) or death, but may also include neurological deterioration without change on imaging. The reported phenomenon of 'pseudo-progression', or a radiological appearance consistent with progression that subsequently improves spontaneously, makes TTP a less reliable endpoint than overall survival.[17]

Six-month progression-free survival

Six-month progression-free survival (PFS) is becoming widely used as an endpoint in brain tumour clinical trials[18] although there are no available published data on the use of this endpoint. Important points to consider for use of six-month PFS as an endpoint include:

- a requirement to standardise frequency of radiologic evaluation

- consideration of use of both neurological and radiological progression as events
- ensuring that only patients with documented disease progression are eligible to enter the clinical trial.
- blinding of reviewers to the intervention allocation group
- the phenomenon of 'pseudo-progression' may make six-month PFS more unreliable as a surrogate endpoint than overall survival.

Radiological objective response

Standardised response criteria are not well developed for brain tumours, and objective tumour response rates correlate poorly with survival in clinical trials.[19] Usual practice is to measure the area of gadolinium enhancing tumour on MRI; however changes in gadolinium enhancement may reflect alterations in vascular permeability and architecture as well as decrease in tumour volume. The more recent uni-dimensional RECIST criteria that were developed with reference to CT scanning in other solid tumours, do not provide specific guidelines for measurement in brain tumours, and have not been well validated in this group, with comparison between WHO and RECIST responses in 30 patients only.[20,21] The bi-dimensional 'Macdonald criteria' were developed in 1990 as an attempt to address the shortcomings of the WHO criteria for assessment of response in brain tumours.[22] However, these guidelines are based on expert opinion and did not attempt to correlate response with survival or patient benefit. Subsequent investigators have attempted to address this issue, showing that for high-grade gliomas there is good correlation between one-dimensional (RECIST), two-dimensional and volumetric measurements. However, the observation of response using these measurements does not predict survival well; time to progression may be a better surrogate for survival than objective response.[23] For non-enhancing tumours, no imaging or response parameters predict survival.

Imaging characteristics may be altered by changes in corticosteroid doses, radiotherapy, implantable chemotherapy wafers, and radiosurgery. Newer agents such as angiogenesis inhibitors also can affect vascular permeability and the appearance of neuro-imaging. Particular attention should be paid to recording corticosteroid dose at the time of imaging, a strength of the Macdonald criteria. Patients should be maintained on a stable corticosteroid dose at baseline imaging and a partial response should not be recorded where the corticosteroid dose has increased from baseline.

Health-related quality of life

The inclusion of HRQL endpoints in brain tumour clinical trials is important due to the progressive cognitive and physical decline experienced by these patients, and the potential for treatments such as surgery, radiotherapy and chemotherapy to adversely affect HRQL. However, collection of HRQL data may be challenging and concurrent use of corroborative proxy HRQL data should be considered.[24]

Validated tools for measurement of HRQL are available for use in patients with brain tumours. Such tools include the Functional Assessment of Cancer Therapy-General (FACT-G) and brain module (FACT_Br)[25] and the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire–core questionnaire (EORTC QLQ-C30) and brain cancer module (BCM-20).[26] Patients with high-grade gliomas and good performance status (such as those enrolled on clinical trials) can comply with the requirements of HRQL collection.[27]

Cognitive function

Measures of cognitive function are important and should be included in randomised clinical trials, however the best tools to use for measurement are unclear and there is no accepted 'gold standard'.[28,29] Neurocognitive deterioration may precede progression on imaging[30] and is also a strong independent predictor of survival[31]. Simple tests such as the Mini Mental State Examination are

insensitive in this population.[29] The role of cognitive function endpoints in earlier phase trials is unclear. Measurement of neurocognitive functioning and resourcing for this aspect of a clinical trial are challenging for investigators. Both progression of disease and treatments (surgery, radiotherapy) may lead to deterioration in cognitive function.

Correlative studies in clinical trials in patients with brain tumours

Consideration should be given to tissue collection and bio-banking for future molecular profiling in clinical trials in patients with gliomas at diagnosis and recurrence. Autopsy studies may provide additional information.

Key points for astrocytomas and oligodendrogliomas:

- Eligible patients should be offered clinical trial participation or referred to a centre where clinical trial participation is available.
- The ethical principles of written informed consent should be carefully considered in patients with cognitive impairment, receptive dysphasia, or impairment of judgment.
- Multidisciplinary involvement in a trial management committee is recommended for clinical trials in gliomas.
- The use of several corroborative endpoints such as six-month progression-free survival, radiological response, cognitive function, and health-related quality of life are recommended for clinical trials in gliomas, however overall survival is the most robust endpoint.
- Validated tools should be used for measurement of neurocognitive function and health-related quality of life.
- Clinical trials in glioma should include central review of histopathology and radiological endpoints.
- Consideration should be given to collection of tissue for biobanking and at autopsy in clinical trials.

Recommendations	Level	References
Time to progression is a better surrogate for survival than objective radiological response and should be incorporated as an endpoint in clinical trials.	III	23
Patients in clinical trials should be stratified for known important prognostic factors.	III	9
Central specialised neuro-pathology review must be incorporated into therapeutic clinical trials in brain tumours.	II	14
Validated health-related quality of life (HRQL) tools are available and should be used where measurement of HRQL is planned.	III	25,26

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4 CLINICAL PRESENTATION

The presenting symptoms of gliomas are determined by several factors including the tumour's size, location and rate of growth. A small tumour deep in the dominant hemisphere may produce significant neurological deficits whereas a tumour in the non-dominant frontal lobe may reach a very large size before becoming symptomatic. A low-grade glioma grows slowly as an infiltrating tumour but a glioblastoma multiforme is an aggressive tumour that in general grows rapidly as a mass. Although a glioblastoma multiforme may arise de novo, it may develop from a lower-grade glioma that has dedifferentiated. A more rapidly growing tumour is more likely to create symptoms of raised intracranial pressure than one that grows more slowly.

Gliomas may present with symptoms of raised intracranial pressure or with focal neurological symptoms that reflect the location of the tumour within the brain. Patients commonly have more than one symptom at presentation. After the initial presentation, family members or friends may report other symptoms that in retrospect they have noticed in the preceding weeks or months prior to the diagnosis, such as subtle cognitive changes. Patients with multi-focal gliomas may have symptoms and signs arising from more than one area of the brain. Low-grade gliomas and high-grade gliomas have different patterns of presentation; in particular, the incidence of seizures differs between tumour types (*see Table 4.1*).

Table 4.1 Proportion of cases presenting with specific symptoms[1–8]

Presenting symptom	Low-grade glioma (%)	Glioblastoma multiforme (%)
Headache/signs of increased intracranial pressure	5–53	19–34
Hemiparesis	20–26	14–41
Seizure	78–89	17–31
Cognitive deficits	11–39	15–22
Speech deficit/aphasia	*	6–32
Visual disturbance	*	3–15
Ataxia	*	9
Cranial nerve dysfunction	*	9
Dizziness	*	9
Loss of consciousness	*	4
Focal neurological deficits	31	*
Transient events	5	*

* prevalence unknown

4.1 Symptoms of raised intracranial pressure

4.1.1 Headache

There have been numerous studies addressing the nature of headaches in patients with brain tumours but there are no studies that have examined headaches only in patients with gliomas. These studies have included patients with different types of primary brain tumours, as well as patients with brain metastases but they are still relevant as they are essentially examining the types of headaches that are produced by a tumour mass in the brain. The one caveat is that the incidence of posterior fossa tumours in these studies is greater than usually occurs in adult patients with gliomas. More modern

studies have the advantage over older studies of improved neuro-imaging techniques (see *Chapter 5 Imaging).*

The classical description of a brain tumour headache[9,10] is one that starts in the early morning and disappears soon after the patient gets up. It is initially mild but then becomes progressively more severe, frequent and of longer duration, and eventually becomes almost constant. It is typically worse with the Valsalva manoeuvre, and is associated with nausea and vomiting. More recent studies however have shown that this type of headache occurs in only a small proportion (17%) of patients.[11]

Headache characteristics

Forsyth and Posner[11] demonstrated that the commonest headache type was a tension-type headache (77% of patients). Nine percent had a migraine-like headache, and 14% had a mixture of headaches that could not be easily classified. The tension-type headaches were described as a dull ache, pressure or like a sinus headache, usually bifrontal but worse on the side of the tumour. The patients with migraine-like headaches all had atypical features, and all had other neurological symptoms or signs. Suwanwela et al[12] also showed that in most patients (74%) the headache was dull and aching, and throbbing in 26%. Rushton[13] found that 58% of patients had constant headaches, and 14% had throbbing headaches; some patients had mixed types of headaches, and in others they were unable to classify the headaches due to inadequate information. By contrast, Pfund[14] found that only 16% of 139 patients with brain tumours had tension-type headaches and 7% had migraine-like headaches, and that the headaches were throbbing in 63%, and shooting in 38%.

Timing of the headache

Forsyth[11] found that the headache was worse in the morning in 36% of patients, worse at night in 17%, worse during the day in 13%, and in 34% there was no clear variation in headache intensity during the course of the day. Rushton[13] found that 25% occurred during sleep or arising, 43% occurred at any time, 2% occurred in the afternoon or evening, and in 30% the time of onset could not be determined. Suwanwela[12] found that 18% had early morning headache, 20% had headache upon arising, and 71% had nocturnal headache. Pfund[14] found that headache occurred upon rising in 14%, in the morning in 32%, nocturnally in 27%, and were variable in 27%. It can be concluded that there is no typical daily rhythm to brain tumour headaches.

Constancy of the headache

Brain tumour headaches are intermittent in 62–88% of patients.[11–14] Pfund[14] found that the headache occurred daily in only 11% of patients, but it was progressive in 79%.

Aggravating factors

The headache can be worse with bending over in 18–32%[11,13]. Suwanwela[12] found that a change in body position, especially arising from bed, aggravated or brought on the headache in 20%. Headaches worsened with the Valsalva manoeuvre in 18–30%.[11–13]

Nausea and vomiting

Nausea or vomiting is present in 36–60% of patients.[11–14]

Severity of headache

The headache is moderate to severe in most patients, but in some (10–20%) was only mild.[11–14] In Forsyth's study[11] headache was the worst symptom in 45% of patients.

Effectiveness of simple analgesics

Simple analgesics are effective in moderately to completely relieving the headaches in 30–58% of patients.[11–13]

Site of the headache

Forsyth[11] found that the commonest headache site was the frontal region (68%), seen primarily in supratentorial tumours or in patient with raised intracranial pressure. They could not reliably differentiate supra- and infratentorial tumours based on headache location, although infratentorial tumours usually had increased intracranial pressure. Pfund[14] showed that 73% of patients with infratentorial tumours had frontal, temporal or parietal headaches, and 24% had nuchal and occipital headaches. In most patients the site of the headache does not assist in localising the tumour. Localisation of the tumour based on the site of the headache is best in those patients who do not have evidence of raised intracranial pressure. Headaches are unilateral in 25–30%[11,12], and they are ipsilateral to the tumour particularly if there is no raised intracranial pressure. Headaches are more common with infratentorial than with supratentorial tumours.[12,14]

History of prior headaches

Forsyth[11] found that patients who had a history of prior headache were more likely to have headaches with a brain tumour. In 36% the brain tumour headache was identical to their previous headache, but was more severe, more frequent, or associated with other symptoms or signs, suggesting either a focal lesion or raised intracranial pressure. Rushton[13] found that 18 of the 132 brain tumour headache patients they studied had a past history of headache that in recent months had changed character and was associated with the development of other symptoms due to their tumour.

Headache as an isolated symptom

In a prospective study Vasquez-Barquero[15] found that only 15 of the183 patients (8%) with intracranial tumours had headache as their first and only symptom; by the time of tumour diagnosis, only one of these 15 still had only headache at the time of diagnosis. In Forsyth's study[11], only 57% of patients had neuro-imaging primarily because of headaches.

Cause of brain tumour headache

Brain tumour headache is related to the size of the tumour and amount of midline shift, which produces traction on pain-sensitive structures such as blood vessels, dura and certain cranial nerves.[9,11,16] Obstruction of CSF pathways may lead to hydrocephalus which may also cause headache.

Neuro-imaging for patients with headaches

In patients with a past history of headache, neuro-imaging should be performed if there is a change in character or pattern of the headache, or if there is the development of focal neurological symptoms and signs. A patient with new onset or recurrent headache uncharacteristic for that patient should also be imaged, particularly if there are focal neurological symptoms and signs.[11,13,14,17]

Recommendation	Level	References
A patient with new onset or recurrent headache uncharacteristic for that patient should also be imaged, particularly if there are focal neurological symptoms and signs.	III	11,13,14,17

Plateau waves

Plateau waves are paroxysmal episodes of neurological dysfunction caused by a sudden rise in intracranial pressure.[18] They may occur spontaneously or be precipitated by the Valsalva manoeuvre or by standing up, particularly in the morning.[19] Episodes last between five and 20 minutes. The commonest symptoms are headache, restlessness, altered consciousness, and sudden weakness of the legs with collapse and without loss of consciousness. Other symptoms include confusion, blurred

vision, ophthalmoplegia, clonic movements of the limbs and urinary incontinence.[18] Plateau waves are due to an increase in cerebral blood volume that is due to a sudden decrease in cerebral vascular resistance.[20,21] They may be mistaken for seizures or transient ischaemic attacks. They may lead to cerebral herniation, respiratory arrest and death.

4.2 Focal neurological symptoms

4.2.1 Brain tumours and cognition

Likelihood of a brain tumour presenting with cognitive deficits

Cognitive deficits in patients with brain tumours can be caused by the tumour itself; by tumour-related epilepsy; by the treatment of the tumour and its effects (surgery, radiotherapy, anti-epileptics, chemotherapy, or corticosteroids); or by psychological distress.[22] More likely, a combination of these factors will contribute to cognitive dysfunction.

Patients with brain tumours can present with cognitive complaints and deficits. Although presentation with cognitive deficits alone is uncommon, subtle cognitive dysfunction is often found in patients with rapidly growing, high-grade tumours. Tucha et al studied the incidence of cognitive impairment among patients with brain tumours, immediately after diagnosis but before the commencement of treatment, by performing a battery of neuropsychological tests on 139 patients.[23] They found that 91% of 126 patients displayed significant impairments in at least one area of cognition. For 71% of the patients, neuropsychological assessments revealed impairments in three or more areas of mental performance. For one third of the patients, impaired functioning in eight or more cognitive areas was observed. Results from other studies in patients with high-grade glioma also indicate that the tumour itself is an important contributor to cognitive deficits.[24] Klein *et al.* assessed cognition in 68 newly diagnosed patients with high-grade glioma and found all exhibited signs of cognitive impairment. These deficits could at least be partly explained by impaired visual and motor functions.

Cognitive deficits and tumour progression

Cognitive deficits may also be caused by recurrent tumour and assessments of cognition have been shown to be a valid method of monitoring for tumour progression. A study of 56 patients with tumour progression found that cognitive deterioration occurred six weeks prior to radiographic failure on MRI whereas reports of deterioration in quality of life and activities of daily living occurred after radiographic progression.[25]

Cognitive deficits and tumour histology

The relationship between tumour histology and cognitive dysfunction has been studied but no clear correlation has been identified. An early study reported that the profiles of the patients with the highest grades of malignant cerebral tumours (anaplastic astrocytomas (AA), glioblastoma multiforme (GBM), and metastatic carcinoma) demonstrated greater cognitive impairments that patients with more slowly growing tumours (astrocytoma grade I and II, ependymoma, oligodendroglioma, or tuberculoma).[26] In this study however, the two groups were not aged matched, the higher-grade tumour group being significantly older that the low-grade tumour group. Also, no estimates of tumour size (area) or volume were presented. Kayl et al compared the neuropsychological functioning of 24 patients with GBM and 24 patients with anaplastic astrocytoma.[27] The groups were matched for age, gender, education as well as tumour location and tumour volume. Analysis of co-variance as well as multiple regression and correlation analyses failed to find any relationship between tumour type, tumour volume and neuropsychological test scores. The authors concluded that tumour histology is not clearly predictive of cognitive performance in adults with GBM and AA.

Likelihood of a brain tumour being the cause of dementia

A retrospective study from a tertiary care memory clinic assessed the prevalence of potentially reversible dementias and whether the cognitive dysfunction improved or resolved after treatment.[28] Of

196 cases that presented with definite or suspected dementia 45 (23%) were found to have a potentially reversible cause. Of these, only two cases (1%) were found to be due to brain tumour. Clarfield undertook a meta-analysis of 32 studies involving 2889 subjects that investigated the prevalence of various causes of dementia.[29] Particular attention was paid to potential and actual reversibility. Of the 2889 cases of dementia, 42 (1.5%) were found to be due to cerebral tumours. Only 11 of the 32 studies provided adequate details of follow-up to assess reversibility. Eleven percent of cases of dementia reversed in part (8%) or fully (3%). Of the 11% of cases that reversed, only 4% (n = 4) were attributed to brain tumour.

4.2.2 Seizures

Likelihood of seizures in a patient with a brain tumour

The overall incidence of seizures in patients with brain tumours is up to 35%.[30] The most common pathologies in patients with recurrent seizures and brain tumours are ganglioglioma and low-grade astrocytoma. Significantly less common are oligodendroglioma, mixed glioma and dysembryoplastic neuroepithelial tumour (DNET).[31–33] A study from the Cleveland Clinic in patients with seizures as the only symptom of primary brain tumour found ganglioglioma in 38%, low-grade astrocytoma in 33%, oligodendroglioma in 10%, low-grade glioma in 5%, and 5% were DNET.[33] In a different series of patients with epilepsy and a low-grade cerebral tumour, ganglioglioma was the most frequent pathology (45%), and seizures in this group commenced at a younger age than patients with other low-grade tumours.[34]

The likelihood of a patient with a primary cerebral tumour experiencing recurrent seizures relates to tumour histology. Although still unexplained, various tumour types have different epileptogenic potential. Studies suggest that patients with cerebral tumours presenting with seizures were more likely to have a low-grade tumour and a normal examination.[30] In a review at the Montreal Neurological Institute, the highest seizure incidence was for patients with oligodendroglioma (92%), astrocytoma and meningioma had a seizure incidence of approximately 70%, and there was a 35% seizure incidence in patients with glioblastoma. This finding has been borne out by other studies.[35] Although uncommon as a tumour type, ganglioglioma is associated with recurrent seizures in almost all patients.[36] Patients with seizures were also more likely to have a cortical tumour location.[37]

The natural history of seizures associated with brain tumours is that of a stable seizure frequency and long duration of epilepsy at the time of surgery.[31,35,38] At presentation these seizures were focal in 40%, and generalised or secondarily generalised in 50%. However in patients with persisting epilepsy, 74% of patients had focal seizures, whereas only 19% had generalised or focal and generalised seizures. Late onset seizures are uncommon, with only 14% of patients developing seizures after diagnosis and first tumour treatment.[37] Thus in patients without initial seizures, the probability of developing epilepsy is low.

Likelihood of a brain tumour in patient presenting with seizures

The incidence of brain tumours in patients with medically refractory epilepsy has traditionally been reported as only 3.5% of patients with epilepsy.[39] This figure may be artificially low, however, as this and many other studies were performed before the advent of MRI. More recent studies have placed this proportion at 10–15%.[33,38,40,41] A Danish study has found the incidence of cerebral tumours in patients with epilepsy diagnosed after the age of 25 was 16%.[42] The incidence rises further when patients are selected from a centre with an active surgical treatment program for intractable epilepsy, and is up to 23% in patients with temporal lobe epilepsy.[32,35,43] This increase is more likely to reflect referral patterns rather than an increase in incidence of cerebral tumours *per se*.

In patients presenting with a first seizure, the incidence of a primary brain tumour ranges from 6% to 12%.[44,45] The proportion of cases varies in part depending on referral patterns and patient selection. Patients presenting with a first seizure should have adequate neuro-imaging with MRI (see *Chapter 5 Imaging*).

Key point:

- Patients presenting with a first seizure should have adequate neuro-imaging with MRI.

4.2.2 Other focal neurological symptoms

As discussed earlier, brain tumours can present with any focal neurological symptom. Although patients with brain tumours typically present with a history of symptoms going back days, weeks, months or even years, in some patients symptoms can come on fairly acutely, and the presentation can be confused with a cerebral infarct or transient ischaemic attack. All patients who present with focal neurological symptoms (such as hemiparesis, dysphasia, dysarthria, neglect, hemianopia, dressing apraxia) require neuro-imaging to establish the cause of these symptoms.

Key point:

- All patients who present with focal neurological symptoms (such as hemiparesis, dysphasia, dysarthria, neglect, hemianopia, dressing apraxia) require neuro-imaging to establish the cause of these symptoms.

Genetics of gliomas

Most gliomas arise as a consequence of acquired somatic mutations of unknown cause in genes responsible for control of cell growth and proliferation. Most of these genetic alterations result in disruption of oncogenes, tumour suppressor genes, DNA repair genes and cell death genes and affect three main cellular systems: RB1, p53 and tyrosine kinase receptor pathways. Other genetic alterations promote mitotic signal transduction, cell cycle regulation, apoptosis, angiogenesis and cell invasion. Most gene alterations induce cell-cycle dysfunction at a complex molecular level.[46,47]

Most anaplastic oligodendrogliomas and oligoastrocytomas have a characteristic genetic alteration with a deletion of the short arm of chromosome 1 (1p) with or without loss of the long arm of chromosome 19 (19q). These alterations are associated with superior survival and potentially with an increased likelihood of response to chemotherapy.[48]

Inherited genetic syndromes are responsible for a few percent of gliomas.[49]

4.2.3 Inherited predisposition to gliomas

Neurofibromatosis

Central nervous system tumours seen in neurofibromatosis type 1 (NF1) include optic nerve gliomas (particularly in children) and other astrocytomas (cerebral or spinal) as well as meningiomas. The condition is inherited in an autosomal dominant fashion and affects one in 3000 individuals. The NF1 is a very complex tumour suppressor gene that sits on chromosome 17 and codes for the neurofibromin gene.[50] Skin signs include neurofibromas, axillary and groin freckling and café au lait (hyper-pigmented) spots. Other characteristic features include Lisch nodules (hamartomas of the iris), intellectual disability and scoliosis. Many with the condition have subtle features only (skin signs) while others are more severely affected (intellectual disability or optic glioma /astrocytoma). Those with neurofibromatosis type 2 classically have bilateral acoustic neuromas (schwannomas) but can also develop astrocytomas and meningiomas.[51]

Tuberous sclerosis

Tuberous sclerosis (TS) affects one in 5000–10,000 individuals and classically causes epilepsy and intellectual disability as well as a variety of skin signs. However the features of the condition are variable. It is inherited in an autosomal dominant fashion but more than half of cases are new mutations. Classical skin signs include multiple hypo-pigmented patches, shagreen patches (a

shagreen patch is an oval-shaped nevoid plaque, skin-coloured or occasionally pigmented, smooth or crinkled, appearing on the trunk or lower back in early childhood; sometimes seen with other signs of tuberous sclerosis), adenoma sebaceum and subungual fibromas. CNS features include cortical tubers and subependymal nodules. Up to 10% of those with TS can develop a subependymal giant cell astrocytoma.[52]

Li Fraumeni syndrome (LFS)

This condition is due to a germline mutation in the p53 gene. High-grade gliomas occur in patients with this condition, which is inherited in an autosomal dominant fashion. Other commonly seen cancer types include premenopausal breast cancer, bone and soft tissue sarcomas, and acute leukaemias and paediatric cancers, particularly adrenocortical carcinomas. The condition is highly penetrant with 90% of those with the condition having a tumour by the age of 70.[53]

Hereditary colorectal cancer syndromes

Hereditary non-polyposis colorectal cancer (HNPCC) is a hereditary bowel cancer syndrome that is inherited in an autosomal dominant fashion. Apart from colorectal cancer, which is classically right sided and occurs at a median age of 45, other tumour types seen include uterine cancer and less commonly, stomach cancer, ovarian cancer, small intestinal cancer, biliary /pancreatic cancer, transitional cell carcinoma of the lining of the upper urinary tract (TCC ureter), and high-grade glioma (the last in 1–2% of cases).

Familial adenomatous polyposis (FAP) is an autosomal dominant condition and can predispose to the development of primary brain tumours. These are typically medulloblastomas but can be gliomas.[54]

Turcot syndrome is the association between familial adenomatous polyposis or hereditary non-polyposis colorectal cancer and brain tumours like medulloblastoma and malignant glioma.[55]

Hereditary glioma

Rarely, families are described in which two or more first- or second-degree relatives have had high-grade gliomas. The pattern of inheritance is either autosomal recessive or autosomal dominant.[56]

Key points:

- Consider referral of patients with glioma to a clinical genetics service if the patient or their first- or second-degree relatives have features or family history suggestive of neurofibromatosis type 1 or tuberous sclerosis.
- Consider referral of patients with high-grade gliomas to a Cancer Genetics Service/Familial Cancer Clinic if there is a personal or family history (first- or second-degree relatives) of premenopausal breast cancer, sarcoma, acute leukaemia or paediatric cancer, especially where two or more of these other cancer types have occurred and where one or more cases have occurred before age 45.
- Consider referral of patients with high-grade gliomas to a Cancer Genetics Service/Familial Cancer Clinic if there is a personal or family history (first- or second-degree relatives) of bowel, uterine, stomach, ovarian, biliary/pancreatic or small intestinal cancer or TCC of the upper ureter, especially where two or more cases of these other cancers have occurred, and/or where one or more of these have been diagnosed before age 50.

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5 IMAGING

5.1 Introduction

Neuro-imaging is an integral component of adult glial tumour management and has many roles to play. This chapter uses the World Health Organization (WHO) tumour grading system for glial tumours.[1] Over the past three decades, there has been a change from invasive techniques which often demonstrated tumours by indirect means, to advanced cross-sectional imaging modalities which now directly illustrate these lesions. Computed tomography (CT) and magnetic resonance imaging (MRI) currently form the mainstay of brain tumour imaging.

Across Australasia there has been a progressive trend to centralise neuroscience resources, mainly relating to the deployment and localisation of neurosurgical services. All units have access to MRI in both the public and private sectors. The aims of imaging of brain tumours are primarily to diagnose or refine a suspected diagnosis and then to optimally localise and characterise them. It is important to assess for potentially life-threatening changes that may necessitate the use of more emergent treatment. An imaging diagnosis of a brain tumour may be the result of the assessment of a clinical syndrome. Screening examinations are only performed in those at high risk of developing a brain tumour such as neurofibromatosis and other familial or genetic syndromes.

Clinicians require CT and/or MRI imaging in order to plan treatment. This maybe used with specialised neuronavigation equipment to facilitate stereotactic localisation of the tumour. This enables the most accurate surgical biopsy or resection and/or radiotherapy treatment for the patient. This and other specialised MRI sequences can be used to help delineate tumour from vital structures such as eloquent cortex, arteries and cranial nerves, and assist in planning treatment, such as positioning the craniotomy and defining the resection margins. Following initial management, CT and MRI can also be used to quantify therapeutic response, assess the extent of residual tumour and detect tumour progression or recurrence as well as recognise effects of treatment and complications such as haemorrhage, contusion and infection. Delayed treatment-induced changes, such as radiation necrosis and leukoencephalopathies, may also cause deterioration in a patient's condition, and be difficult to differentiate from tumour progression on imaging grounds.

This chapter reviews the imaging of glioma from the technology available for lesion diagnosis, through to surveillance and follow-up. Recommendations are made as to the appropriate imaging protocols, based on the current literature and teaching hospital standards. There is an inherent problem with constructing evidence-based guidelines in radiology, in part because of the rapidly evolving technology in CT, MRI and also nuclear medicine techniques. The levels of evidence as they are currently described for academic and clinical medicine are not tailored for imaging science and those currently available cannot and must not be applied to current imaging practice.

Key points:

- Neuro-imaging is an essential component of glial series tumour management.
- CT and MRI form the mainstay of tumour imaging.
- The main aims of imaging of brain tumours are to:
  - primarily diagnose or refine a suspected diagnosis
  - optimally localise the lesion
  - characterise the lesion
  - assess the lesion's secondary effects and complications
  - plan surgical and radiation treatment including the provision of input data for neuronavigation
  - quantify therapeutic response
  - recognise post-treatment progress and complications

5.2 Routine imaging modalities

Historically, plain skull radiography, echoencephalography, early forms of radionuclide brain scanning, pneumo-encephalography and angiography were amongst the imaging methods used to indirectly diagnose intracranial space-occupying lesions.[2,3] Today, these modalities are no longer employed in the assessment of brain tumours, apart from angiography when uncommonly, a neuro-interventional procedure is contemplated as part of a patient's management.

5.2.1 Computerised tomography

CT is usually the preliminary investigation when clinical symptoms and signs raise the suspicion of the presence of an intracranial mass. CT is widely available and is relatively fast and inexpensive compared with MRI. In addition to confirming the presence of a space occupying lesion and/or possible brain tumour, CT is helpful in demonstrating the presence of intra-tumoural calcification which may suggest an oligodendroglial series lesion; as well as assessing those that may have haemorrhagic components or skull vault or base involvement.

On CT, glial tumours are mostly of low attenuation with variable enhancement patterns depending on the pathological grading. Atypical lesions may be multifocal and/or have increased attenuation on the unenhanced studies. On the other hand, lesions of higher-grade may not necessarily enhance. This is an imaging feature of anaplastic astrocytoma.

The use of iodinated intravenous contrast media in tumour imaging assists in detection and characterisation. Higher doses of contrast administration are associated with increased lesion conspicuity.[2,4] Demonstrable enhancement in the mass reflects an increase in local tumour vascularity and contrast leakage from the intravascular compartment due to a disruption of the blood–brain barrier. In the presence of a glial tumour, contrast enhancement is associated with a higher pathological grade of tumour.

MRI is contraindicated in patients with ferromagnetic aneurysm clips, cardiac pacemakers, cochlear implants and intra-orbital metallic foreign bodies. Alternative CT protocols, employing multi-channel systems and volumetric imaging with multi-planar reconstructions may however suffice for the initial and subsequent evaluation. CT volumetric studies can also be used as the basis for neuronavigation

imaging data, when the lesion and/or target is readily visible on CT. A CT angiogram (CTA) may also be useful if the lesion is in close proximity to intracranial vessels, as an aid to pre-surgical planning.

CT has several limitations; soft tissue resolution of CT images is inferior to that of MRI, in certain regions of the cranial cavity, such as the middle and posterior cranial fossae, artefacts limit lesion visibility and therefore interpretation, and iodinated contrast has a risk of hypersensitivity reactions.

5.2.2 Magnetic resonance imaging

All intracranial lesions needing an intervention such as biopsy or resection should have evaluation by MRI. The technique is superior to CT in many respects as it has excellent soft tissue contrast resolution, multi-planar capabilities and does not require the use of ionising radiation. Lesions are more conspicuous and therefore are detected with greater sensitivity than with CT which has a comparative sensitivity and specificity of 87% and 79% respectively.[3] There is, however, no difference in detection of surgical space-occupying lesions between CT and MRI.[5] Differing tissue components (intra-tumoural heterogeneity) are more likely however to be characterised with MRI, as is the extent of the tumour. The technique is therefore the preferred modality in subjects in whom brain neoplasia is a possible diagnosis.

Modern mid magnetic field (1–1.5 tesla) clinical MRI systems produce diagnostic-quality images in a reasonable time frame. Multi-planar imaging should be performed in all cases to determine the best surgical approach and to delineate relationships with important structures as well as changes associated with the mass effect resulting from the lesion.

The use of contrast is imperative to verify components of the tumour and must be used to assist in grading and local staging. As with CT, enhancement in the tumour matrix reflects an increase in the local tumour vascularity and a disrupted blood–brain barrier, indicating a higher pathological grade of tumour. Contrast enhancement will help to identify significant extra information such as meningeal and ependymal involvement as well as intracranial metastatic disease. Gadolinium-based contrast media also has a safer risk profile than that of iodinated contrast.

The main aim of the MRI study is to confirm the diagnosis of an intracranial space-occupying lesion and more importantly, to refine the diagnosis, detect additional findings not seen on the CT, and help plan more accurately the surgical approach. The majority of lesions are hypo-intense on T1 weighted imaging, and hyper-intense on T2 studies. Again, there is variable enhancement depending on the grade. A variety of signals can be seen within lesions resulting from necrosis, proteinaceous material or haemorrhage.

A basic reproducible MRI protocol is as follows:

a. Fast/turbo spin echo axial T2 weighted study

b. Spin echo sagittal or coronal T1 weighted study

c. Spin echo sagittal, coronal and axial T1 weighted study following the administration of intravenous gadolinium contrast media

Additional sequences that may help in the lesion evaluation include:

a. Fluid Attenuated Inversion Recovery (FLAIR) studies: A T2 weighted study with CSF suppression which increases lesional conspicuity[6–8] (Class IV evidence)

b. Fat-saturated contrast-enhanced studies are helpful for tumours close to the skull base or calvarium

c. Magnetic resonance angiography and venography may assist for lesions closely associated with the intracranial vasculature

d. Susceptibility weighted/T2 weighted gradient echo studies more readily identify those tumours with haemorrhagic components

e. Diffusion imaging (see advanced and emerging imaging modalities)

f. Perfusion imaging (see advanced and emerging imaging modalities)

g. MR spectroscopy (see advanced and emerging imaging modalities)

h. Magnetisation transfer imaging also assists with lesion conspicuity.[4,9]

i. Volumetric imaging with multi-planar reconstructions should be performed on MRI to allow accurate neuronavigation for surgical and radiotherapy interventions (see later). This may include MP-RAGE (magnetisation prepared rapid gradient echo), SGPR (spoiled gradient echo) or volumetric T2 or FLAIR acquisitions.

Many of these additional sequences that should or could be added to the basic MRI protocol are of interest and may provide additional information. However there is no strong evidence that they improve the cost-effectiveness of outcome in the patient being investigated for a suspected brain tumour.

MRI technology and scanning comes at a significant increased cost compared with CT and is not as widely available. In addition to specific medical contraindications to MRI, patients experiencing claustrophobia may require general anaesthesia or sedation. Furthermore, the evaluation of bony involvement and calcified or haemorrhagic components is better on CT.

Key points:

- CT (with or without the use of intravenous contrast) because of its ready availability is most often the first examination to reveal the possibility of an intracranial neoplasm.
- CT also helps also with the assessment of calcified and haemorrhagic lesions as well as those that may involve bone.
- CT requires the use of x-rays (ionising radiation).
- Contrast-enhanced MRI is the imaging modality of choice for the diagnostic workup of an intracranial lesion because of its superior soft tissue resolution and multi-planar imaging capabilities.
- MRI has a greater accuracy in lesion depiction compared with CT.
- MRI is contraindicated in patients with ferromagnetic aneurysm clips, cardiac pacemakers, cochlear implants and intra-orbital metallic foreign bodies.

5.3 Diagnostic and pre-operative imaging considerations

In patients presenting with neurological syndromes, deciding who should undergo brain imaging to exclude a neoplasm is difficult and the evidence is limited. Patients with neoplastic brain disease most commonly present with headaches, seizures and/or focal neurological deficits. However in the individual patient, the clinical presentation will often depend on the lesion topography.[10,11] The gradual or even relatively acute onset of a clinical syndrome that progresses over time is a helpful

indicator, with emphasis on the progressive nature of the symptomatology. No combination of clinical symptoms and signs reliably differentiates brain tumours from other benign aetiologies.[12]

Imaging can be used to exclude an alternative tumefactive non-neoplastic process, such as infarcts[5,13] (subacute, venous), aneurysms, haematomas[6,14], cavernous malformations, abscesses[7,15], granulomatous lesions, demyelinating lesions[16–22] and other inflammatory pseudo-lesions such as plasma cell granuloma. Surgical intervention may therefore be either modified or avoided. Non-anatomic physiological imaging methods may also be helpful here. These include MRI diffusion, perfusion, and spectroscopy.[23–25]

Age and lesion location are important and may help in predicting tumour type. Despite the appearances on MRI and CT, for the vast majority of lesions the ability to predict tumour type reliably remains limited. The final diagnosis is made on histopathology. Presumed radiological diagnosis is only used to guide non-surgical treatments when surgery is likely to cause significant neurological deterioration. Examples of these circumstances would be radiotherapy and chemotherapy for brainstem and optic pathway glioma.[8,26]

Neuroradiologists and neurosurgeons must use accurate diagnostic techniques that confirm characteristics of individual glial neoplasms before recommending specific treatments. Ideally, all patients who are considered to have a presumptive diagnosis of a glial series tumour should be managed by a multidisciplinary team in a centralised neurosciences centre.

Neuroscience centres must be capable of providing emergency imaging facilities when called for and able to accommodate patients requiring a general anaesthetic, and the waiting times for brain tumour patients must be appropriate. For non-urgent cases, a one-week period to complete imaging evaluation is thought to be acceptable.

Scanning should be supervised by an accredited MRI and/or neuroradiologist. Ideally, all scans performed outside of the neurosciences centre should be reviewed by the neuroradiological team before treatment.

Compared with other human tumours, the diffuse cerebral glioma is unique in that the imaging, in part, reflects histopathological and clinical behaviour.[9,27] Low-grade gliomas (LGG) are usually a focal expansion of neuroparenchyma, with minimal surrounding white matter change and no contrast enhancement, whereas high-grade gliomas are more space occupying, contrast enhancing and cause notable surrounding white matter oedema.

Gliomas, particularly high-grade lesions, are also often disseminated at the time of diagnosis, with tumour cells being detected beyond the margins of the radiographic lesion.[28]

Histological intra-lesional heterogeneity is a feature of glial series tumours, with extremes of grade, biological behaviour, gene expression and MR signals sometimes represented in different areas of the same lesion.[29–31] This heterogeneity may be demonstrated or implied by advanced imaging methods, such as MR spectroscopy and perfusion imaging. Foci of high-grade tumours may be demonstrated in areas that do not contrast enhance and therefore this feature of the tumour cannot be reliably used for diagnosis or follow-up. Contrast-enhancing portions may also over- or under-estimate the presence of active tumour. With this in mind, even if a biopsy specimen is low grade, the presence of contrast enhancement should alert the clinician to the possibility of a high-grade component to the overall lesion. This warrants attentive follow-up or further surgical intervention to obtain more diagnostic material.[32]

Low-grade glioma (LGG) will grow slowly in size, with a significant proportion undergoing anaplastic progression to a high-grade glioma (HGG) (also known as secondary GBM).[33–36] This may be seen as increasing T2 change, heterogeneity and contrast enhancement.

Key points:

- No combination of clinical symptoms and signs reliably differentiate brain tumours from benign causes.
- MRI and CT cannot reliably predict tumour type; biopsy and histological assessment are required.
- Standardised tumour imaging protocols are necessary.
- The timing of imaging must be appropriate to the patient's clinical state.
- Scanning should be supervised by an accredited MRI and/or neuroradiologist.
- Ideally, all scans performed outside of the neurosciences centre should be reviewed by the neuroradiological team prior to treatment.
- Gliomas, particularly high-grade lesions, are heterogeneous structurally and are disseminated at the time of diagnosis.
- Contrast-enhancing portions may either over- or under-estimate the presence of active tumour.
- Low-grade glioma (LGG) will grow slowly in size, with a significant proportion undergoing anaplastic progression.

5.4 Tumour imaging appearances

The classical appearance of GBM or grade IV tumours is an irregular nodular-ring-enhancing lesion which has mixed attenuation and signal characteristics on CT and MRI respectively. The lesions are usually of low attenuation on CT and of high signal on T2 and low signals on T1 weighted MR imaging. The central non-enhancing component is indicative of cavitation or necrosis. The enhancement may be of relatively increased attenuation or of low signal on T2 weighted studies, indicating hypercellularity. There maybe both neoplastic or associated cysts present, and a variable amount of surrounding 'infiltrative' oedema which is a combination of increased interstitial water, and neoplastic cells. The tumour tends to infiltrate along white-matter tracts and perivascular spaces, allowing distant spread with little disruption to the brain.

Low-grade gliomas (LGGs) are poorly defined, low attenuation lesions with minimal mass effect and surrounding oedema. In a majority of cases there is no contrast enhancement. The lesions are of low signal on T1 weighted studies and of high signal on T2. Their visibility and definition is better on T2 weighted imaging. While the typical imaging features of a LGG can often be present, LGG cannot be diagnosed on imaging alone. An exceptional situation arises with lesions such as brain stem and optic pathway gliomas, where the appearances may be very typical and given the risks of biopsy, adjunctive treatment is often commenced on the basis of imaging appearances alone.

Oligodendroglial tumours have a similar appearance, but may be located more superficially, are very commonly calcified and contain areas of cystic degeneration. These lesions show slight or moderate enhancement with intravenous contrast media.

Key points:

- Glial tumours can have imaging characteristics that allow diagnosis and an estimation of pathological grade, however there is significant overlap and inconsistencies that limit accuracy of diagnosis. Biopsy is therefore required.
- The appearances of brain stem and optic pathway gliomas may be very typical and given the risks of biopsy, treatment is often commenced on the basis of imaging appearances alone.

5.5 Radiological report

Ideally, the interpretation and reporting of neuro-oncology should be performed by neuroradiologists and cross-sectional imaging specialists who have a dedicated interest. Reliable and standardised reporting and review at a centralised unit allows for more comprehensive pre-operative and ongoing patient management.

A suggested report should include:

1. Identification of factors that may limit the sensitivity and specificity of the examination.
2. Confirmation of presence of a neoplastic lesion.
3. Whether the abnormality is multicentric
4. Imaging characteristics: uniform or variable
    i. T1 and T2 signal characteristics.
    ii. Contrast enhancement.
    iii. Presence of haemorrhage and necrosis.
    iv. Presence of tumour or associated cysts.
    v. Infiltrative or vasogenic or cytotoxic oedema.
5. Three-dimensional lesion size, defining what is being measured, for example, contrast-enhancing portion or T2 change.
6. Anatomical locality.
7. Secondary phenomena:
    i. Mass effect, brain shift and herniation syndromes.
    ii. Infiltrative or vasogenic or cytotoxic oedema.
    iii. Generalised brain swelling.
    iv. Presence of haemorrhage and necrosis.
    v. Presence of hydrocephalus.
8. Incidental findings.
9. Comparison with previous examinations (or reports if images not available).

10. Comments: indicating conclusions of the study, including a differential diagnosis and suggesting an appropriate follow-up imaging protocol.

If there are features such as brain shift or herniation that may warrant emergency management, it is recommended that the concerns of the radiologist be directly conveyed to the referring physician so that early intervention can be considered.

Key points:

- Reporting of neuro-oncology should ideally be performed by neuroradiologists.
- The radiological report is a dynamic phenomenon and may change with additional clinical or ancillary information.
- More structured and standardised reporting is recommended.
- If there are features that warrant emergency management, this should be directly conveyed to the referring physician as soon as possible.
- It is important to assess and document tumour response to treatment.

5.6 Surgical neuronavigation and intra-operative imaging

Another important function of brain imaging is to optimally localise the tumour prior to surgery. In addition to routine imaging, 'neuronavigation' has become an important adjunct technique in many neurosurgical procedures. The central concept of accurately 'projecting' CT or MRI data into the operative field allows the surgeon to optimise anatomical orientation, better defining anatomical landmarks, optimally positioning a minimally-sized craniotomy flap, and allowing precise targeting of pathological structures and tumour margins during operative procedures. Neuronavigation may also be used for frameless stereotactic biopsy for deep seated lesions where tumour debulking is not possible.[10,37] Pre-operative MRI should include stereotactic data to reduce the need for repeat imaging.

With an average intra-operative 'error margin' of approximately 3–4mm, neuronavigation allows a more aggressive resection in a greater proportion of cases and hence the achievement of significantly lower relative residual tumour volumes. This has been shown to be associated with better neurological and functional patient outcome, with a significant prolongation in survival.[38–40] There is improved surgical safety by minimising adjacent tissue trauma during procedures.[11,41–43]

Relatively recent technological developments have led to the manufacture of a variety of MRI units that can be used intra-operatively, providing the surgeon with real-time updated imaging during a surgical procedure and integrating this with navigation capabilities. The systems have been shown to improve the extent of resection and increase the proportion of patients in whom complete removal of the enhancing parts of the tumour can be achieved.[44] Studies of intra-operative MRI have revealed that the surgical objective is not achieved in up to one third of initial unguided resections.[17,45]

Recent studies have suggested an association between the extent of surgical resection and survival for neurosurgical patients who underwent surgery for low-grade glioma with intra-operative MRI assistance. The greater the resection, the longer the survival recorded.[46,47–49] Intra-operative MRI is not yet widely available in Australia. Surgery utilising this technique for patients with grade IV gliomas has not been convincingly demonstrated to be more efficacious than conventional methods. [50]

Key points:

- 'Neuronavigation' projects CT and/or MRI data into the operative field for better anatomical orientation, better defining of anatomical landmarks, better positioning of the craniotomy flap, and precise targeting of pathological structures and tumour margins during operative procedures.
- Intra-operative MRI can compensate for brain shifts and therefore allows a better assessment of the extent of resection.

5.7 Post-operative assessment

Most patients with intracranial neoplastic lesions will have some form of operative intervention, whether it is a biopsy, partial resection, gross total resection, or even a lobectomy. In LGG there is some evidence that radical surgery does lengthen survival and improve quality of life[24,51], however given the infiltrative nature of glioma lesions, complete resection is rare. CT is routinely used at some institutions in the early post-operative period to exclude complications such as haematomas and cerebral swelling that may not be clinically evident. Other institutions only image if there is a clinical indication. Scans can also be assessed for any gross remaining tumour and it is common practice to use contrast-enhanced imaging.

Post-surgical enhancement can be seen along the resection margins on approximately the third and fourth post-operative days. It is usually represented as fine linear, sometime amorphous, nodular changes and therefore can make the assessment for residual or recurrent tumour challenging. Dural enhancement is sometimes seen at the craniotomy site. This can last up to six months.[52,53]

An early post-operative MRI within the first 24 to 48 hours can be used to assess the operative site for residual tumour. With MRI, treatment-related contrast enhancement can be seen as early as 18 hours post-operatively, but usually does not appear in the first three to four days. This can been seen for longer with MRI than with CT, and has occasionally been seen beyond one year following the surgical intervention.[53,54] Scanning in the early post-operative period will also allow assessment with diffusion imaging (*see section 5.8 Follow-up imaging*) to assess any contribution of parenchymal damage to subsequent changes seen in the brain. Haemorrhage is also less likely to interfere with the visualisation of residual contrast-enhancing tumour on the immediate post-operative study.

MRI is the preferred modality to assess the post-operative status of the brain. As with CT, contrast enhancement on subsequent imaging can lead to a false interpretation of residual tumour or recurrence and it may take weeks to resolve a question of treatment-related changes versus tumour if early scanning is not performed. The method used to assess for residual tumour is based on evaluating for contrast-enhancing structures. It should be kept in mind that there may be significant components of tumour, either low or high grade, but which do not exhibit enhancement. Therefore while using contrast enhancement as the basis of defining residual tumour is imprecise, it is the basis of clinical practice. Review of the pre-operative imaging may help to identify the imaging characteristics peculiar to the tumour, which may help in subsequent interpretation. New foci and clumps or nodules of enhancement associated with extending T2 changes are however more likely to represent tumour. With evolving post-surgical changes, haemorrhage and parenchymal damage, progressive tumour may be difficult to exclude in the first three post-operative months. It is important to maintain standardised imaging protocols that include the utilisation of gadolinium to lessen the difficulties with interpretation of subsequent or follow-up imaging.

Dural enhancement and thickening in relation to the surgical site is common and even remote dural changes may present. The question of infection is sometimes raised, however imaging is a poor discriminator and often the decision is a clinical one. Dural enhancement may persist for years.

In the early post-operative period, imaging may also be performed for the purposes of guiding subsequent radiotherapy if indicated.

Key points:

- Reactive post-operative changes can be seen as early as 18 hours on MRI and can last for years.
- Immediate post-operative imaging may help to differentiate between residual tumour, post-operative reactive changes and parenchymal damage as a result of treatment.
- Contrast-enhanced MRI is more sensitive in detecting changes compared with CT, however it still has limitations, notably with high-grade non-enhancing lesions.
- Adherence to standardised imaging protocols is advised to aid in the interpretation of subsequent follow-up studies.

5.8 Follow-up imaging

Part of the ongoing care of the oncology patient is imaging to monitor for treatment response and tumour recurrence or progression, and to assess for any possible treatment-related side effects. No adequate data exist on the role of imaging in the monitoring of brain cancer response to therapy, even though this constitutes a substantial part of neuro-oncology imaging.

Given the sensitivity of MRI in demonstrating components of gliomas in pre-operative studies, its use has now become routine. CT can be used but may be insensitive to early progressive changes if early intervention is to be considered.

The optimal frequency of these follow-up studies is unknown. Much of common imaging practice is based on protocols extrapolated from neuro-oncology trials[55–59] or empirical clinical practice. Apart from any immediate post-operative scan, the first baseline examination is usually performed between six weeks and three months after the completion of definitive treatment, then at 2–3 month intervals. If the disease is found to be stable, the intervening interval may be increased to 6 months. If however, there are equivocal findings that may indicate a significant change, an early interval scan should be prescribed, for example at 4–6 weeks. In the event a patient develops new symptoms, an earlier examination should be undertaken.

Despite a much more favourable outlook when compared with high-grade glial series tumours,[60] routine imaging surveillance of LGG is prescribed to monitor for the signs of malignant transformation. In the long term this is thought to occur in approximately 50% of lesions and is more likely in the elderly.[61] The volume of T2 hyperintensity is the strongest predictor of overall survival of patients with supratentorial diffuse astrocytoma (WHO II) and the only predictor of malignant progression.[62] This may be seen as a new focus of progressive T2 signal change or contrast enhancement. Alternatively, a gradual growth pattern is seen. Oligodendroglioma have been noted to grow in diameter by about 4mm per year.[63] Serial follow-up MRI examinations are performed every 3–6 months as a supposed standard of practice.[64]

A variety of imaging protocols is employed in follow-up studies, however it is important to maintain the same protocol to allow accurate comparison. The number of sequences can be minimised by utilising those that will demonstrate any worrisome changes, such as extension of signal change and new or progressive contrast enhancement.[65] The appearances may be complicated by evolving post-treatment changes.

One of the major limitations is the detection of changes that may indicate a response to treatment and the ability to differentiate them from those indicating progressive tumour growth. Contrast-enhanced

MRI usually fails to detect the effects of radiotherapy and chemotherapy at least in the first 12 months.[66–68] A reduction in contrast enhancement and T2 changes on MRI may be interpreted as an imaging improvement and is assumed to be a treatment response, but these findings are non-specific and may be due to a variety of processes. Comparison should be made with the most recent historical study; however extending the comparison to scans in the distant past may help to clarify subtle changes when suspected. This may include surveying the original imaging.

The description of the lesion on follow-up studies should include a measurement of tumour size. However, quantifying this can be difficult. Lesions are often irregular in outline, heterogeneous in grading, and have significant necrotic and cystic components. In addition, the contrast-enhancing portion may not be representative of the tumour as a whole. Orthogonal diameters of the contrast-enhancing component/s taken through the lesion on the trans-axial scans have nevertheless been the process by which objective tumour measurements are made. From this an approximate area or volume can be calculated. Summary data illustrating the location of measurements will help with inter-observer variability when reporting further examinations. Computer-aided volumetric analysis has been shown to be more reliable and better at detecting early progression. Perimeter measurements have however been found to be the most sensitive measure of treatment response.[69,70]

For the purposes of clinical trials, the radiological response is a timelier indicator than survival, particularly for phase II therapeutic drug trials. This however is reliant on the assumption that an imaging response is a valid surrogate measure for improved survival. Clinicians must realise that measuring a change in tumour diameter, area or volume seems potentially an insensitive means of detecting early treatment response. Classifications for treatment response that are used in phase II and III clinical trials for malignant glioma include the MacDonald[71] and RECIST criteria. See *Chapter 3 Clinical trials and research* for further discussion.

Given the progressive nature of HGG with a maximum reported two-year survival rate of 26.5%[72] , complete or partial responses are rare. Progression-free survival (PFS) period, that is, the duration of stable disease, has been used as alternative method of assessing efficacy in several trials.[73,74] However there is less evidence with GBM that radiographic response is suitable as a surrogate marker for survival.[75] Assessment may be complicated by pseudo-progression seen after treatment.

The changes associated with treatment, usually radiotherapy, can be illustrated on both CT and MRI. Radiation can cause significant damage to astrocytes and vessels, resulting in a breakdown of the blood–brain barrier. Acute oedema may be visualised. Radiation-induced demyelination and necrosis can be seen as early as three weeks to three months.

Delayed radiation damage usually becomes evident between six months and two years, but can occur many years following treatment. Radiation necrosis is an uncommon irreversible progressive necrotic mass which is often identical in appearance to that of progressive residual or recurrent HGG and often mistaken for progressive disease.[76] The appearance of radiation necrosis on CT and MRI is that of irregularly lesions, with nodular, linear, or curvilinear, ‘soap bubble- ’ or ‘Swiss cheese-like’ patterns of enhancement.[1,9,77,78] Both radiation necrosis and residual tumour however rarely exist as distinct entities but more often in combination as a single lesion. However there is often a predominating process. No adequate data are available on the role of imaging in differentiating between tumour recurrence and therapy-related changes. Routine anatomic imaging is usually unhelpful; however metabolic imaging has a suggested theoretical advantage in the differentiation. This includes forms of SPECT and PET imaging, and MR spectroscopy (MRS). There is, however, insufficient evidence supporting the routine clinical use of these modalities in this clinical setting (see later sections).

A necrotising leukoencephalopathy is seen in association with chemotherapeutic agents but this is more common in children than adults. Other entities such as mineralising angiopathy, large-vessel occlusion, telangiectasia, meningioma and other secondary tumours may occur rarely.

Key points:

- The aim of follow-up imaging is to monitor for treatment response, tumour recurrence or progression and to assess for any possible treatment-related side effects.
- No adequate data exist on the role of imaging in the monitoring of response to therapy of gliomas but nevertheless this forms a significant part of neuro-oncology imaging.
- MRI is the best imaging modality for the follow-up of glial series tumours, however the optimal frequency of these studies is unknown. Based on neuro-oncology trials, apart from any immediate post-operative scan the first baseline examination is usually performed between six weeks and three months after the completion of definitive treatment, then at two to three month intervals. If the disease is found to be stable, the interval may be increased to six months.
- The difficulty in distinguishing between changes that may indicate a response to treatment and those indicating progressive tumour growth are important limitations of follow-up imaging.
- Follow-up neuro-oncology imaging protocols should be standardised.
- A description of the lesion on follow-up studies should include an objective measurement of tumour size.
- Radiation necrosis is an uncommon irreversible progressive necrotic mass which is often identical in appearance to that of progressive residual or recurrent HGG and exists more often in combination with residual tumour. No adequate data are available on the role of imaging in differentiating between tumour recurrence and therapy-related changes.

5.9 Advanced and emerging modalities

Over the past two decades there has been a vast array of research within radiology using advanced imaging technologies and their application in the neurosciences. This has been particularly evident in MRI and nuclear medicine. The components of MRI that have been applied to neuro-oncology include MRS, diffusion imaging, perfusion imaging (which can be performed on CT also), and blood oxygenation level-dependent functional MRI (BOLDfMRI). These entities no longer specifically address anatomical pathology but rather pathophysiological changes in disease. A summary of their applications is provided in Table 5.1 below. These techniques have been implemented in the work-up of patients with brain tumours, however there is no high-level evidence in the literature indicating better outcomes or improved cost-effectiveness in the patient being investigated for a suspected brain tumour.

Key points:

- Forms of advanced MRI that have been applied to neuro-oncology include MR spectroscopy (MRS), diffusion imaging, perfusion imaging and BOLD fMRI.
- Patho-physiological changes are the focus of these techniques in disease.
- There is no high-level evidence indicating better outcomes or management cost-effectiveness when using these techniques.

Table 5.1 Advanced imaging modalities

Modality	Potential indications	References
MRS	Refinement of pre-operative differential diagnosis	15,79–82
	Biopsy site selection	81,83,84
	Monitoring treatment response	85
	Differentiating tumour from treatment effects	86
	Lesion extent	
Perfusion imaging	Angioneogenesis (cerebral blood volume) Tumour grade Radiation changes versus tumour	87–92
	Microvascular permeability Tumour grade	93–95
Diffusion imaging	Refinement of pre-operative differential diagnosis, including abscess differentiation.	96–99
	Pre-operative information: fibre tractography Apparent diffusion coefficient (ADC) Diffusor tensor imaging (DTI)	100–103, 104–109
	Monitoring treatment response: Apparent diffusion coefficient (ADC) Diffusor tensor imaging (DTI)	104–109
	Monitoring treatment response: convection therapy	106,107
fMRI	Pre-operative information: eloquent cortex localisation	110–117
	Neural reorganisation	118

5.10 Nuclear medicine

Historically, nuclear medicine assumed a significant role in the diagnosis of intracranial disease using ^{99m}Tc DTPA labelled isotopes. This did include tumour detection, but with the advent of direct cross-sectional imaging modalities such as CT and MRI, the routine use of nuclear imaging studies in brain tumour diagnosis has been superseded. There is an extensive body of research initiatives and there are some specific clinical problems for which scintigraphy may have a role in the management of patients in some centres.

Modalities such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) may help with the understanding of tumour pathophysiology and metabolism. Both these modalities have improved contrast and spatial resolution compared with two-dimensional techniques. Significant improvements have also been made in co-registering functional images with anatomical studies obtained on CT and MRI. This has increased the sensitivity from 65 to 85%.

The tracer most commonly used in SPECT imaging of the brain today is Thallium (^{201}Tl). This has a limited role in clinical management, but maybe helpful in pre-operative grading of the lesion or in differentiating between recurrent high-grade glioma and radiation-induced necrosis.[119] There is considerable overlap between grades of tumour[120] and other entities such as strokes, scars and meningiomas.[121] The histology of post-radiotherapy brain is usually mixed, with components of tumour as well as reaction to radiation and surgical injury. The additional clinical information provided by this form of scintigraphy over that provided by MRI and histology is debatable.[122]

At a cellular level, PET studies can demonstrate increased cell proliferation. There is a variety of radioactive tracers, of which^{18}F- fluorodeoxyglucose (^{18}F FDG) is the most commonly used, and illustrates foci of increased glucose metabolism.[123–129] Increased metabolic activity is a feature of high-grade gliomas, and FDG-PET can help distinguish low-grade from high-grade lesions pre-operatively, as well as evaluate the extent of tumour infiltration, find an appropriate site for biopsy[130–133] and demonstrate malignant transformation in low-grade lesions. In the last situation, a new hypermetabolic focus may appear. The presence of ^{18}F FDG uptake has been shown to be an independent prognostic risk factor.[134–137] The limitations of ^{18}F FDG imaging include the high background activity of the normal brain and the raised activity exhibited by some low-grade lesions such as pilocytic astrocytomas, gangliogliomas, and oligodendrogliomas.

PET differentiate recurrent tumour from radiation necrosis with a moderate sensitivity and specificity of 75% and 81% respectively.[138]

Another labelled PET isotope used is ^{11}C Methionine. This is associated with less background parenchymal activity and therefore has increased specificity and sensitivity[137,139–143], highlighting foci of cellular proliferation correlating well with the histological stain Ki-67, and with microvascular density.[144,145] The intensity of uptake correlates with neoplastic grade of the lesion and can therefore be used to determine a suitable site for biopsy and to define the extent of tumour for radiotherapy planning.[146] Oligodendrogliomas exhibit marked uptake as does ischaemic and inflammatory change, which limits the specificity of this isotope.[131,146–148] This form of PET can be used to assess treatment response.[149]

A number of new isotopes traces are being investigated, but their role is yet to be defined.

Key points:

- With the availability of CT and MRI, the use of nuclear imaging studies for brain tumours is no longer routine.
- The use of scintigraphy is limited to research protocols and some specific clinical indications in centres with appropriate expertise.
- Thallium (^{201}Tl) is the most frequently used isotope in neuro-SPECT, and may be helpful in pre-operative grading of the lesion and differentiating between recurrent high-grade glioma and radiation-induced necrosis.
- Fluorodeoxyglucose (^{18}F FDG) is the most commonly used isotope in neuro-PET. This may have a role in pre-operative grading, evaluating the extent of tumour infiltration, finding an appropriate site for biopsy, and detecting malignant transformation in low-grade lesions.

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6 DIAGNOSIS AND PATHOLOGY

6.1 Introduction

Definitive diagnosis of a brain tumour requires histological examination of representative tissue from the lesion by a qualified and experienced pathologist. Diagnoses based on clinical and or radiological findings alone should be viewed as presumptive and should not form the basis for definitive treatment or further clinical management unless there are compelling clinical considerations that preclude biopsy.

Tissue should be removed from the patient, processed and examined in ways that optimise the formulation of an accurate diagnosis. The resulting pathology report should include a determination of the tumour type (astrocytoma or oligodendroglioma) and the tumour grade, and should comment on any other prognostic or predictive features identified.

The histological diagnosis of brain tumours should be undertaken by a neuro-pathologist or by an appropriately trained anatomical pathologist with some experience in tumour neuropathology.

6.1.1 Clinical data

Adequate clinical information should be included with the pathological specimen and is essential for correct diagnosis. This is probably most necessary when an intra-operative consultation (frozen section) is requested.

As well as demographic data (name, age, and sex), information about the clinical history, the site of the lesion(s), the radiological appearance, and whether there has been previous treatment (eg surgical, radiotherapy, chemotherapy) are necessary in order to provide an accurate diagnosis.

6.1.2 Specimen handling

Fresh tissue for intra-operative diagnosis should be obtained without crushing or cautery artefact and should be transported to the laboratory on a non-absorbent surface (eg Telfa or a non-absorbent plastic jar). Small specimens should not be placed on gauze or cotton wool as the tissue fragments may become entangled and difficult, if not impossible, to extract.

6.1.3 Intra-operative consultation

After macroscopic description, small portions of the fresh specimen should be examined by standard cytological and histological techniques. These may include touch preparations, smears, crush or squash preparations and frozen sections. Areas of differing appearance should be sampled. Common pitfalls, often resulting in suboptimal smear preparations, include:

- trying to smear too much tissue (a 1mm fragment is usually adequate)
- delaying fixation, resulting in air-drying artefacts.

A number of different stains can be used to examine the cytological preparations, including haematoxylin and eosin, toluidine blue, peroxidase-antiperoxidase (PAP) and Diff Quik. The technique(s) adopted will, to some extent, depend on the experience and expertise of the laboratory and the pathologist.

Part of the specimen should be fixed in formalin for paraffin embedding without freezing since freezing frequently introduces significant artefacts that may compromise diagnosis. Fresh tissue should not be placed between surgical sponges prior to fixation as this results in artefactual distortion of the tissue and may compromise subsequent assessment of cellularity.

Ideally *all* tissue removed from the patient should be submitted for pathological examination, including aspirated material and the material from ultrasonic surgical aspirators. Heterogeneity within tumours is well documented and in many brain tumour resections, the material routinely submitted for pathological diagnosis forms only a small part of the actual tissue removed from the patient.

Aspirated tissue fragments, fixed in a large volume of buffered formalin and retrieved by subsequent filtration, are usually well preserved and allow assessment of intra-tumoural variation. In some cases this may result in a change in the tumour grade and subsequent management. It is important that this material remains unfixed in saline for as short a time as possible. The specimen should be received in the laboratory at the end of the operation and should *not* remain overnight without fixation.

When material is being collected for tissue banking it is important to ensure that adequate material is provided for histological diagnosis. A histological diagnosis should take precedence over tissue banking when the specimen is small.

6.1.4 Pathology report

A pathology report should include at least the following information:

- demographic and clinical data
- a macroscopic description of the material received
- a microscopic description
- a diagnosis incorporating tumour type (astrocytic, oligodendroglial) and tumour grade
- identification of any prognostic and/or predictive factors.

A suggested reporting framework is given in Table 6.1. Diagnosis and grading should be based on standardised and validated criteria. While to some extent these vary over time, currently the World Health Organization criteria are the most widely accepted.

Table 6.1 Outline of suggested reporting framework

Demographic and clinical information	Patient identification and demographic data (age, sex)
	Clinical information
Frozen section	Whether part of the sample was frozen and/or used for intraoperative diagnosis
	Whether information was conveyed to the surgeon
Macroscopic description	Number of different specimens received
	Specimen labels or other identification
	Whether the specimens were received fresh or in formalin
	Type of specimen received (fragments, cores or lobectomy)
	Specimen dimensions (individual fragments and total)
	Appearance and consistency of material
	The proportion of the specimen processed paraffin sections including number of blocks
Microscopic description	A brief histological description of the material documenting the presence or absence of diagnostic features
	Tumour cell lineage (eg astrocyte vs oligodendrocyte)
	Tumour grade
	Cellularity
	Cytological atypia
	Mitotic figures
	Necrosis
	Vascular proliferation
	Infiltration into other tissues
	Treatment effects
Diagnosis	Diagnostic classification based on World Health Organization criteria
	Numerical grade and grading system (eg WHO grade II)
Comment	This may include information about the representativeness of the specimen (eg a single stereotactic biopsy core from a large mass), the presence of prognostic or predictive features, or suggested further investigations (eg genetic analysis or referral for a second opinion).

6.1.5 Grading

Although there is a gross correlation between proliferation, as measured by the MIB-1/Ki-67 proliferation index, and clinical outcome, there is some overlap in proliferation index between diffuse and anaplastic astrocytoma, anaplastic astrocytoma and glioblastoma, and oligodendroglioma and anaplastic oligodendroglioma. Consequently, in an individual case, the Ki-67 labelling index cannot be used to assign tumour grade. However, since grade II and grade III astrocytomas are distinguished

by the presence of mitotic activity in the latter, it has been suggested that MIB-1 labelling indices may more reliably separate grade II from grade III tumours in some situations, especially when only a small specimen is available for analysis.[1]

6.1.6 Prognostic and predictive features

Tumour grade is the single most important prognostic feature (see *Chapter 1 Epidemiology*). Currently there is no validated factor that unambiguously predicts tumour progression from diffuse astrocytoma (WHO grade II) to anaplastic astrocytoma (WHO grade III) and glioblastoma multiforme (WHO grade IV) in individual patients.

6.1.7 Tumour heterogeneity, sampling and inter-observer variation

As in other tumours, morphological and genetic heterogeneity is well documented in gliomas. Only part of this heterogeneity is identified radiologically. Consequently it should be remembered that the material examined and reported on may not be representative of the entire lesion. Correlation with the radiological and other findings is important, especially when the specimen examined is small. For example, a pathological diagnosis of 'fibrillary astrocytoma WHO grade II' for a tumour with significant contrast enhancement suggests a sampling problem.

There is considerable inter-observer variation in the diagnosis and grading of gliomas. This is most marked for the diagnosis of tumours with an oligodendroglial component, including oligodendroglioma (grade II), anaplastic oligodendroglioma (grade III), oligoastrocytoma (grade II) and anaplastic oligoastrocytoma (grade III). This in part stems from the lack of a reliable reproducible marker for oligodendrogliomas. Panel review of anaplastic oligodendrogliomas and anaplastic oligoastrocytomas from the EORTC Trial 26951 demonstrated large discrepancies between the diagnoses provided by the submitting local pathologists and those provided by an independent panel of nine neuro-pathologists. For anaplastic oligodendrogliomas, a consensus diagnosis was reached in 52% of the cases that were submitted with a diagnosis of anaplastic oligodendrogliomas, and in only 8% of cases that were submitted with a diagnosis of anaplastic oligoastrocytoma. There was also considerable inter-observer variation within the panel of experts.[2]

Review by an expert neuro-pathologist is recommended to reduce diagnostic error.

6.1.8 Genetic testing

Although extensive and ongoing genetic research has increased our understanding of the biology of brain tumours, at present the use of genetic analysis as part of the standard diagnosis and management of brain tumours is more restricted and is somewhat controversial. Due to the rapid and continuing developments in this area, current guidelines are likely to be rapidly superseded.

Currently, genetic analysis does not provide diagnostic information but, in certain circumstances, it provides prognostic and predictive information.

6.1.9 1p/19q loss

Although concurrent loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) is identified in up to 80% of oligodendrogliomas, this is *not* a diagnostic criterion for this tumour. The absence of these abnormalities does not exclude the diagnosis of oligodendroglioma.

In anaplastic oligodendrogliomas, the presence of 1p/19q loss is an independent prognostic factor associated with increased survival.[3] 1p/19q status also predicts increased likelihood of a response to therapy, radiotherapy and/or chemotherapy (with procarbazine, CCNU and vincristine [PCV] or temozolomide). Although in WHO grade II oligodendrogliomas, 1p loss with or without 19q loss is associated with prolonged survival, it is unclear whether 1p/19q status predicts treatment response.[4] 1p/19q loss of heterozygosity (LOH) may also be predictive of prognosis for astrocytomas.[5,6]

Since it provides prognostic information, genetic testing for loss of 1p/19q is recommended for all tumours with an oligodendroglial component.

The commonly used techniques for identifying 1p and 19 q allelic loss, namely fluorescence in situ hybridisation (FISH) or loss of heterozygosity (LOH) analysis, appear to have similar sensitivities and specificities. A disadvantage of LOH analysis is that is requires a specimen of the patient's non-tumour DNA, usually from a blood sample. This complicates retrospective analyses or the use of archived material.

6.1.10 Testing of glioblastomas for MGMT promoter methylation

MGMT (O6-methylguanine-DNA methyltransferase) is a DNA repair enzyme that reverses damage brought about by environmental as well as therapeutically administered alkylating agents. Expression of MGMT protein in tumour cells renders them relatively resistant to alkylating chemotherapeutic agents.

Normal cells almost invariably express MGMT protein, whereas many cancer cells do not. It is thought that the absence of MGMT in cancer cells gives them a selective advantage because unrepaired DNA mutations generate cancer cell variants which may have a selective in vivo growth advantage. The selectivity of alkylating agents for tumours is in part related to the differential expression of MGMT protein in normal versus tumour cells.

Expression of MGMT is controlled by the upstream gene promoter. In many cancers examined, lack of MGMT and mRNA expression is related to hypermethylation of cytosine residues (CpG islands) in the promoter region blocking gene transcription, although other mechanisms, including post-transcriptional silencing, have been reported.

Clinical relevance

Silencing of MGMT protein expression, chiefly through promoter methylation, is a recently recognised phenomenon in glioblastomas and is associated with a good response to alkylating chemotherapy, particularly temozolomide (Temodar™, Temodal™), and markedly improved patient survival as compared to glioblastomas expressing MGMT with an unmethylated MGMT gene promoter.[7,8] MGMT promoter hypermethylation occurs in up to 75% of glioblastomas.

The ability of cancer cells to express MGMT is assessed by tests for MGMT promoter hypermethylation, for example, methylation specific PCR (MSP) or methylation-sensitive high-resolution melting of PCR amplimers (MS-HRM), either alone or in combination with immunostaining for MGMT protein.

In Australia, at present, the decision to give temozolomide to patients with glioblastoma is rarely influenced by knowing the MGMT status of the tumour, as MGMT testing is seldom performed, despite the fact that some clinical data support such testing.[7,9] MGMT testing may not become routine in the management of patients with glioblastoma until the biological mechanisms whereby promoter methylation affects tumour behaviour are clarified and the results of larger clinical trials are known.

Although it is common practice to treat all patients with glioblastomas with temozolomide, as the drug has an excellent therapeutic effect, in some patients knowing that the MGMT promoter is not methylated in tumour cells may influence the decision to discontinue treatment if there is little or no response.[10] Discrepancies in the laboratory testing of MGMT also need to be assessed and rectified.

6.1.11 Tumour tissue banking

If available and following informed consent from the patient, consideration should be given to depositing part of the specimen not required for diagnosis in a tumour bank. Serum should be collected at the same time as the tissue is collected to optimise translational research opportunities.

Tumour banks also require a clinical dataset to accompany each specimen. This will facilitate brain tumour research and will provide an important resource that facilitates better understanding of the biology of brain tumours for improved diagnosis and treatment in the future. Brain tumour banks are operating in most Australian capital cities.[11]

Key point:

- The histological diagnosis of brain tumours should be undertaken by a neuro-pathologist or by an appropriately trained anatomical pathologist with some experience in tumour neuropathology.
- Ideally *all* tissue removed from the patient should be submitted for pathological examination, including aspirated material and the material from ultrasonic surgical aspirators.
- A pathology report should include at least the following information: demographic and clinical data; a macroscopic description of the material received; a microscopic description; a diagnosis incorporating tumour type (astrocytic, oligodendroglial) and tumour grade; and identification of any prognostic and/or predictive factors.
- A histological diagnosis should take precedence over tissue banking when the specimen is small.

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7 LOW-GRADE ASTROCYTOMAS

7.1 Introduction

This chapter will deal with the management of low-grade astrocytomas (LGA) only. It specifically will not include the management of low-grade oligodendrogliomas, juvenile pilocytic astrocytomas, pleomorphic xantho-astrocytomas, gangliogliomas and other non-astrocytomatous or mixed glial tumours. It will include a discussion of both adult and paediatric low-grade astrocytomas under separate headings. The authors recognise the controversial nature of this topic and identify several key areas where there is not consensus. The classification of low-grade astrocytomas, the diagnosis, the imaging characteristics, the treatment and follow-up all present interesting polarising schools of thought.

The epidemiology of LGAs is given in *Chapter 1 Epidemiology*.

7.2 Diagnosis

7.2.1 Clinical presentation

Common presenting symptoms of LGAs include epilepsy, headache, mental changes and focal neurological deficit. Epilepsy is the presenting symptom in more than half of all cases.[1,2] Headache and focal neurological deficit occur less frequently, and signs of raised intracranial pressure with papilloedema are uncommon.[1]

7.2.2 Conventional imaging

Magnetic resonance imaging (MRI) is the imaging modality of choice. MRI is the most sensitive test available to diagnose LGAs. CT scanning is often the initial study performed and in a typical case reveals a non-enhancing low-density lesion. Mass effect upon the surrounding ventricular structures is common. If enhancement does occur, it is generally faint and homogeneous. On the MR images, the lesion typically presents as a low-intensity area on T1-weighted images whereas there is almost always an increased relaxation time on T2-weighted images. The area of increased signal is usually homogeneous and well circumscribed, with no evidence of haemorrhage or necrosis.[3] Enhancement on CT or MRI occur in between 8 and 15% of cases.[4-6]

Despite the general acceptance of standard MRI as the primary diagnostic tool in assessment of LGAs, the classification of gliomas with conventional MRI can be unreliable, with the sensitivity ranging from 55% to 83%[7-11] For instance, Knoop et al[11] showed that almost one fifth of glioblastomas do not show enhancement.

Similarly, tumour cells can extend beyond routine CT and MRI-defined boundaries.[12,13] Tumour margins may be better defined with the use of diffusion tensor imaging[14] (see *Chapter 5 Imaging*).

7.2.3 Advanced MRI techniques

Advanced MRI techniques such as perfusion MR and proton MR spectroscopy (MRS) have found increasing utility in evaluation of glial tumours. Theoretically, the advantage of MRI techniques in evaluating cerebral gliomas is the ability to sample the entire lesion as well as surrounding brain.[15]

It has been suggested that dynamic contrast-enhanced T2-weighted MRI may identify more malignant areas within an astrocytoma.[11] Relative blood volume (rCBV) measurements from dynamic susceptibility contrast perfusion MRI have been shown to correlate with microvascular density in gliomas[16], which are independent prognostic markers for low-grade astrocytomas.[17] rCBV maps and measurements have been shown to correlate with tumour grade.[11,18-28]

Magnetic resonance spectroscopy may have a role in the diagnosis of LGA. Specifically, elevation in choline with depression of N-acetylaspartate (NAA) is a reliable indicator of tumour. Also, there is a considerable literature that shows the metabolite ratios of choline/creatinine, and myo-inositol/creatinine, and the presence of lipids and lactate may be useful in grading tumours and predicting malignancy.[29]

The role of magnetic resonance spectroscopy (MRS) in the diagnosis of low-grade astrocytoma has been controversial. A recent systematic review has evaluated the role of MRS in the characterisation of brain tumours.[29] In relation to LGAs, MRS may aid in differentiating high- from low-grade astrocytoma. Five studies have addressed this issue and four of these showed that MRS was highly sensitive and specific in this regard.[30-34] However the data on the ability of MRS together with regular MRI to accurately predict the nature and grade of glial tumours is questionable. In addition, there are few studies that use this technology to differentiate LGAs from other lesions that can resemble LGAs on regular imaging.

Law et al[35] have assessed the role of rCBV and MRS in the evaluation of cerebral gliomas. Both techniques offer much when attempting to differentiate low- from high-grade gliomas, since when compared to a sensitivity of conventional MRI of 72%, rCBV was 95% sensitive and MRS was approximately 97% sensitive using choline/creatinine and choline/NAA ratios. These authors[36] have suggested that perfusion MRI and MRS may overcome the limitation of sampling error that exists with histological analysis by their ability to sample the entire lesion non-invasively.

Law et al[37] have provided evidence that rCBV provides a better predictor of behaviour of low-grade gliomas (including astrocytomas, oligodendrogliomas and oligoastrocytomas) than histological analysis. These authors point out that histopathological assessment has significant limitations for the following reasons:

- only small samples of tissue are assessed, particularly from stereotactic biopsy, and the most malignant part of the tumour may not be sampled (sampling error)
- obtaining a specimen may be difficult from eloquent brain (any part of the brain that has a defined function, the loss of which will lead to major functional impairment)
- classification systems are inconsistent
- there is significant intra- and inter-pathologist variation in diagnosis
- glial tumours are dynamic and tend to dedifferentiate to higher grades over time. In this study of 35 patients, including 21 with LGAs, rCBV showed a significant negative association with disease-free survival, that is, low rCBV values were associated with longer times to progression. Lesions with rCBV <1.75 had a median time to progression of 4620 +/□ 433 days compared to lesions with rCBV >1.75, where the median time to progression was 245 +/□ 62 days.

Based on their study, Law et al[37] have proposed that rCBV be used as an important factor when deciding on appropriate treatment of LGGs. Primarily, rCBV can be used to decide whether patients should undergo adjuvant radio- and/or chemotherapy after maximal surgery (if rCBV >1.75), rather than observation with serial imaging with a low risk of progression (rCBV <1.75). In addition the authors suggest that with a high rCBV, a more aggressive approach to surgical management could be undertaken in the knowledge that these tumours are likely to progress rapidly.

rCBV and MRS may also have a role in predicting the grade of oligodendroglial tumours.[38]

7.2.4 ADC maps

A recent study has shown that apparent diffusion coefficient (ADC) maps, derived from diffusion weighted images, can show differences between low-grade astrocytomas and oligodendrogliomas.[39]

7.2.5 Positron Emission Tomography (PET)

There may be a role for positron emission tomography (PET) in the diagnosis and treatment of patients with LGA. LGAs are typically hypometabolic and therefore 'cold' on PET scanning. High-grade areas tend to be hypermetabolic and therefore will appear as a 'hot spot' on PET scanning. This information may be valuable in determining the aggressiveness of therapy.[40,41] Different PET methodologies have been used to differentiate low- from high-grade gliomas, including 13N-ammonia PET[42] and methionine[43] with the former showing some ability to differentiate astrocytic from non-astrocytic low-grade gliomas.[42]

Key point:

- Definitive diagnosis cannot be made on imaging alone. The presence or absence of enhancement offers some guidance but is not absolutely specific. Non-enhancing tumours may be high grade. Enhancing tumours may be low grade.

7.3 Management of LGAs

Management of the patient with a LGA starts with compassionate and well-informed delivery of information. It is incumbent on the physician to ensure the patient and family members are informed of treatment options and the controversial nature of these recommendations. Naturally, the doctor may introduce his/her own bias as this is almost impossible to avoid. Responsible informed consent does not preclude personal bias as long as options are given.

Often these cases are reviewed in multidisciplinary brain tumour conferences.

Key points:

- If the patient has been informed of all the pros and cons of a conservative approach and elects to wait then this is reasonable. This option is especially applicable if the tumour is less than 10cm^3 in volume, diffuse on T2 MRI scan and in an eloquent area.
- Once progression has been documented treatment should be offered before the onset of fixed neurological deficits.

Without definitive evidence of the benefit of surgery, an accepted recommendation has been a complete avoidance of surgical intervention. Given that the reliability of biopsy is variable and that current imaging techniques may confer better prognostic information (*see below*) this would appear to be an acceptable option. Patients with diffuse LGA in eloquent areas face some risk of deterioration following a needle biopsy but it is possible to biopsy many low-grade astrocytomas with acceptable risk. The resectability of a low-grade astrocytoma depends very much on its extent and the part of the brain that is affected. The more eloquent brain involved the more difficult it is to obtain a resection without causing significant morbidity. Some patients may understandably find this risk unacceptable. This raises the obvious question of what radiological or clinical changes should provoke a more aggressive approach.

If waiting for tumour growth, what rate of growth is unacceptable and why should delayed surgery be any safer than upfront surgery? If waiting for contrast enhancement, is this not akin to closing the gate after the horse has bolted? If waiting for clinical deterioration, would this not negatively influence quality of life and ultimately the patient's functionality? Therefore, this conservative approach needs to be balanced with the negative effects of waiting. There is some evidence that waiting for tumour progression such as the onset of neurological deficits, growth of tumour and contrast enhancement may negatively affect the time to progression (TTP) and overall survival (OS). The other argument against waiting is that upfront surgery may subject the patient to the potential for neurological deficit

but at least there is a real chance of neurological status quo, whereas waiting for a deficit to develop precludes any chance of being neurologically normal.

7.3.1 Establishing a histological diagnosis

Histopathological analysis is generally considered the gold standard in determining diagnosis and tumour grade. Biopsy, although safe, is not as accurate as open resection in providing specimen for histological analysis. A recent study demonstrated that patients who underwent biopsies, and subsequent resection, had an accurate diagnosis in 76% of cases, and in 91%, biopsy predicted the appropriate therapy.[44] Framed and frameless techniques were equivalent. Although the authors stated that biopsy was accurate in predicting therapy, their own results imply that in almost one in ten patients who underwent biopsy, their therapy would have been different had more specimen been available for analysis.[44]

Stereotactic biopsy has limitations due to sampling error. Jackson et al[45] showed that in almost half of glioma cases, there was a discrepancy in diagnosis between initial biopsy diagnosis and diagnosis after subsequent resection. Therefore when deciding on management options, reliance on limited biopsy information may be misplaced.

Key points:

- Histological diagnosis may be unreliable because of sampling error.
- Pre-operative MR imaging may have a closer correlation with survival than histological grading on biopsy.

7.3.2 Attempt at complete macroscopic resection

All primary glial tumours have indiscrete borders. There is never a capsule and even when there appears to be a well-defined tumour/brain interface, histological studies would suggest otherwise. Terminology in the literature is extremely variable. Authors may be referring to the same situation when they talk about complete removal, near-complete removal, complete macroscopic removal and radical sub-total resection. For the sake of uniformity, we use the term *complete* to describe a resection that results in a post-operative MRI that shows absolutely no residual enhancing or non-enhancing tumour, acknowledging that there are residual tumour cells within the surrounding 'normal' brain; the term *near complete* to describe a >95% resection by volume: and the term *sub-total* to describe a <95% resection.[28]

The first and clear advantage of tumour resection is reduction in the incidence of sampling error. There is also the opportunity of sending tumour for cytogenetic evaluation and tumour banking, both of which have therapeutic implications.

The second and less clear advantage of tumour removal is the ability to achieve a curative resection. Unfortunately, attempts at complete resection, although advocated by many, have been achieved by few, so definitive statements cannot be made. However, complete macroscopic resection may confer a survival benefit. This benefit negatively correlates with the amount of residual tumour; the more residual, the shorter the TTP and OS. There may also be a lower rate of malignant transformation with reduced tumour bulk.[46]

Other indications for surgical resection are for intracranial hypertension, restoration of CSF pathways, improvement of epilepsy and in a few patients, palliation of symptoms.

7.3.3 Technique of surgery for LGA

Standard microsurgical techniques are used for removal of LGAs. The introduction of frameless stereotactic technology, endoscopy, tumour labelling and intra-operative MR imaging, has increased surgeons' confidence, but these tools have yet to make a statistical impact on survival. Awake craniotomy and intra-operative cortical mapping may reduce the risk of permanent post-operative neurological damage but offer no survival advantage. Indeed, the incidence of complete resection is reduced with both these techniques and they may, in fact, negatively affect survival.

7.3.4 Defining degree of resection

Clinical estimate of resection is invariably incorrect. The best method of determining the degree of resection (DOR) is to perform a post-operative MRI scan within 48 hours of surgery. This should be done with contrast medium and any nodular enhancement should be interpreted as residual disease. Linear enhancement around the tumour cavity may be post-operative changes. Of course, if another sequence showed the tumour better pre-operatively then this sequence should be used to determine DOR.

Key points:

- There is definitely a role for attempted resection of a LGA. It should probably be done at the time of diagnosis for the following potential benefits: more accurate diagnosis, palliation of symptoms, extension of survival, reduced chance of malignant transformation and possible cure.
- Recommendation of resection should be tempered if the tumour is diffuse, located in an eloquent area or less than 10cm^3 in volume.
- Standard microsurgical techniques should be employed with the addition of stereotactic guidance if available.
- Awake surgery or cortical mapping are optional but may reduce the incidence of post-operative neurological deficit if the aim of surgery is to palliate and secure a diagnosis rather than prolong life or achieve a cure.

7.3.5 Unique sub-types of LGAs

Brainstem LGA

Brainstem LGAs can be found in children and adults. Most brainstem gliomas are malignant and the juvenile pilocytic sub-type (JPA) is seen in the paediatric population. JPAs usually enhance relatively uniformly, whereas the malignant glioma exhibits patchy enhancement. The treatment algorithm is similar to other brainstem tumours. If the tumour is focal, attempt at surgical resection may be considered. This has resulted in improved long-term survival and a significant incidence of cure.[47] If the tumour diffusely enlarges the pons, despite having low-grade features, no surgical intervention is recommended.

Tectal LGA

LGAs located in the tectum of the midbrain behave uniquely. They are typically extremely slow growing or remain quiescent for entire lifetimes. Indeed, their biological inertia has led some to label these lesions as hamartomas. They present with hydrocephalus from secondary aqueduct stenosis necessitating treatment of the hydrocephalus only. The recommended treatment is endoscopic third ventriculostomy. Shunting may be required if this operation fails. Biopsy or resection of the tumour is indicated when there is discernible growth or new contrast enhancement. There is an association with Neurofibromatosis Type 1 (NF1).

Optic pathway/hypothalamic LGA

These have also been associated with NF1 but can occur sporadically. They are more commonly seen in children and can present early (<3 yrs of age) or late. Most tumours in this area are LGAs but there is a more aggressive variety, the pilomyxoid type, which occurs in younger children, presents with hypothalamic dysfunction and has a higher incidence of recurrence. Surgical intervention is reserved for those patients in whom there is CSF obstruction, and clinical or radiological progression despite all other attempts to inhibit the tumour's growth. The aim of surgery, given the high-risk location, is to achieve a radical but sub-total resection.

7.4 Adjuvant therapy of low-grade astrocytoma

Once biopsy or resection has allowed histological confirmation of the diagnosis of low-grade astrocytoma (LGA), the question of adjuvant treatment must be addressed. Many LGA patients will be well and asymptomatic post-surgery, and any additional treatment thus requires careful consideration of its benefits, such as improving overall survival, in comparison to potential toxicity.

7.4.1 Radiotherapy

Based on current available evidence, radiotherapy remains the gold-standard adjuvant therapy. The major issues in relation to radiotherapy are optimal timing, optimal dose, volume to be treated, benefit of additional chemotherapy, and toxicity, particularly the contribution of radiotherapy to the long-term neurocognitive problems experienced by many patients with LGG.

LGA is undoubtedly a radio-responsive disease. Although response assessment using conventional criteria (radiological/clinical evidence of complete response, partial response, stable disease, progressive disease) is not common in radiotherapy studies, there are other data supporting the sensitivity of LGA to radiation. Retrospective studies showing an apparent survival advantage for radiotherapy[48-50] cannot be regarded as definitive confirmation, with selection bias a concern. However, compelling evidence has been provided by the EORTC study 22845[51] in which 311 adults were prospectively randomised to initial post-operative observation or to radiotherapy. Patients in the radiotherapy arm had a significant benefit in progression-free survival (PFS), with median PFS of 5.3 years in the early radiotherapy group versus 3.4 years in the initial observation group (hazard ratio 0.59, p<0.0001), and five-year PFS of 44% and 37% (p=0.02), respectively. Seizure control at one year was also noted to be superior in the radiotherapy arm (41% versus 27%). Despite this evidence of response to radiotherapy and improved progression-free survival, the study did not demonstrate a significant survival advantage for early radiotherapy, with median overall survival (OS) in the radiotherapy group 7.4 years compared with 7.2 years in the initial observation group (hazard ratio 0.97, p=0.872). Sixty-five percent of patients in the initial observation group had radiotherapy at the time of progression, and the equivalent overall survival in this group suggests that LGA is equally responsive to radiation in the delayed setting. Based on these results, consensus opinion is that for the majority of LGA patients, an initial policy of observation post-surgery is appropriate, with treatment being deferred until there is clear radiological or symptomatic progression. The policy of initial observation is not appropriate for patients with high-risk features (EORTC prognostic score 3–5, see Table 7.1), who demonstrate early progression and poor median survival. These patients should proceed to early radiotherapy. LGA in the brainstem represents another special category. Because of its rarity, the published literature is small, but most patients are symptomatic at presentation and unsuitable for resection, thus early radiotherapy is appropriate.

The question of radiotherapy dose has been addressed in the EORTC study 22844[52], and the Intergroup study conducted by the North Central Cancer Treatment Group (NCCTG), the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Group (ECOG).[53] These studies randomised 211 and 379 adults respectively to low- (□50Gy) versus high-dose RT (59.6 or 65Gy). There was no difference in the five-year OS or PFS rates between the two dose groups in either study,

and the rate of complications such as radiation necrosis was higher in the high-dose group. Current consensus is that a dose of 45–50Gy represents the optimal balance between efficacy and toxicity.

The volume of brain irradiated in LGA patients has progressively decreased over the past two decades. Early stereotactic biopsy studies demonstrated that tumour cells frequently extended beyond imaging abnormalities, and the subsequent use of large margins to define radiotherapy target volumes resulted in essentially whole-brain radiotherapy for many patients. However, later prognostic factor analysis showed no improvement in outcome for larger volumes[54,55], and indeed there was evidence that larger volumes were associated with an increased risk of neurocognitive disability.[56-58] Analysis of patterns of failure in the EORTC Study 22845,[52] in which margins were 1–2cm beyond the imaging abnormalities, demonstrated that over 90% of recurrences were within the irradiated volume. Thus there appears to be no rationale for chasing microscopic disease beyond the obvious imaging abnormalities, and a conformal approach, using margins of 1–1.5cm only beyond the T2-defined MRI abnormality, is recommended. The use of stereotactic radiotherapy or interstitial brachytherapy does not appear to improve LGA outcomes beyond those of standard conformal techniques.[59]

The potential for debilitating radiation-related late toxicity, particularly neurocognitive deficits, is of great concern in a population where prolonged survival is common. Although surgery[60], chemotherapy[60] and use of anti-epileptic drugs[58] have all been demonstrated to result in complications including impaired neurologic function, the development of neurocognitive deficits in LGA patients has usually been attributed to radiotherapy. Radiotherapy to the brain has certainly been shown to be associated with radiological evidence of white matter changes, specific cognitive deficits, and radiation necrosis. The risk of radiation necrosis is very low but is not clearly established and appears dose-dependent[53] and it is rarely fatal. There is no evidence that radiotherapy results in an increased risk of high-grade transformation of LGA.[52]

It is uncertain whether radiotherapy causing significant neurocognitive disability in LGA patients is problematic.[61] The limited evidence of neurocognitive side effects is almost exclusively retrospective, and includes studies in which many patients were treated with techniques that are no longer standard. There are intrinsic biases in some studies, and the interaction between total dose, dose fraction, treatment volume, use of chemotherapy, tumour recurrence, pre-existing neurologic morbidity, and the development of neurocognitive deficits, is not well studied. Crossen's review[57] of patients treated with therapeutic brain radiation in 29 studies found that 28% had some degree of late encephalopathy attributed to radiation, with severity related to patient age, total dose of irradiation, fraction sizes, and timing of chemotherapy. Klein's multi-centre study of 195 patients with low-grade glioma[58] also found the use of radiotherapy to be associated with poorer cognitive function; however, cognitive disability in the memory domain was found only in radiotherapy patients who received fraction doses exceeding 2Gy. This study also compared quality of life and cognition in low-grade glioma patients treated with either early or delayed radiotherapy, with those of a control group suffering from haematological malignancies. Both low-grade glioma groups had significantly worse cognitive function than the control group. It may be that the tumour itself, and particularly tumour progression, is the major determinant of cognitive function, rather than radiotherapy.[62] This is supported by an extensive literature review by Brown et al[63], which concluded that the weight of evidence suggested only sporadic, limited neurocognitive damage from conformal radiotherapy at the usually prescribed doses for LGG. The limited prospective data available[63-66] show only minor cognitive effects attributable to radiotherapy, although there is a lack of data beyond five years post-radiotherapy. This deficiency is being addressed by the current EORTC prospective study, but results will not be available for some years.

7.4.2 Chemotherapy

The case for chemotherapy in the adjuvant setting is not currently established for LGA. Although responses have been seen with a variety of regimens–CCNU, PCV, temozolomide[67-70]–in small studies in the setting of recurrence or pre-radiotherapy, studies in which chemotherapy has been added

to radiotherapy have not demonstrated additional benefit. A small trial conducted by the Southwest Oncology Group (SWOG)[71] randomised patients to radiotherapy alone (55Gy, n=19) or to radiotherapy plus CCNU (n=35). This trial was stopped early due to lack of accrual, however, there was no significant difference in median survival or response rate between the two treatment arms. Similar results were seen in the randomised trial RTOG 9802,[72] in which 251 patients with unfavourable features (age ≥40 years, subtotal resection/biopsy) were randomised to either RT alone (54Gy) or RT plus six cycles of PCV chemotherapy. There was no improvement in overall survival with the addition of PCV to RT; the chemotherapy arm did demonstrate a significant benefit in progression-free survival, but was also associated with significantly more acute treatment toxicity. A direct comparison of radiotherapy and chemotherapy in the adjuvant setting has not been previously undertaken, but this is currently being investigated in the EORTC study 22033/26033 (RT versus temozolomide).

Key point:

- When no other treatment can be offered and there is clear clinical and/or radiological progression, there is definitely a role for radiotherapy. In the post-surgical setting, its role is less well defined. If surgery offers relief of symptoms and halts progression, then adjuvant treatment can be reserved for progressive disease. If radiotherapy is given immediately after surgery, it will extend TTP but will not extend OS any longer than if given later when the disease progresses. The role of chemotherapy in the treatment of LGAs is unclear.

7.4.3 Prognosis

LGAs have a wide spectrum of outcome, but generally have a period of relative stability for four to seven years before a period of accelerated growth, usually associated with transformation to high-grade astrocytoma.[60] Survival following accelerated growth averages 12 months. Over the past three decades, survival for low-grade astrocytomas has increased.[73]

Favourable prognostic factors include age less than 40 years, seizures as presenting symptom, good performance status and absence of contrast enhancement, with median survival ranging from as little as 12 months for patients aged over 40 years with poor performance status to 128 months for patients aged under 40 years with good performance status.[74] Contrast enhancement confers a worse prognosis as it is more commonly associated with high-grade gliomas and suggests transformation and more rapid growth.

The EORTC reported the largest patient data set to determine prognostic factors for patients with low-grade gliomas (EORTC 22844 and 22845). Three hundred and twenty-two patients in EORTC 22844 were analysed to determine independent prognostic variables, which was subsequently validated on the 288 patients from EORTC 22845 (Table 7.1).[75] Determining an individual's prognosis and estimated time to malignant transformation is crucial to decision-making about timing of intervention versus observation.

Loss of 1p/19q is rare in LGAs, as compared with oligodendrogliomas. Approximately 60% of low-grade astrocytomas have an alteration of the p53 tumour suppressor gene, and although some studies have reported a less favourable prognosis in patients with p53 mutations, results have been conflicting.[76] There does not appear to be an association between p53 status and response to therapy.

Table 7.1 Prognostic variables for low-grade gliomas

Characteristic		Hazard ratio	Median survival (years)
Age, years	<40	1	
	>40	1.26	
Largest diameter of the tumour	<6cm	1	
	>6cm	1.23	
Tumour crossing midline	No	1	
	Yes	1.37	
Histology	Oligodendroglioma / mixed glioma	1	
	Astrocytoma	1.3	
Neurologic deficit	Absent	1	
	Present	1.35	
Score (sum of above factors)		0	9.2
		1	8.8
		2	5.8
		3	3.5
		4	1.9
		5	0.7

Adapted from Lang[75]

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8 HIGH-GRADE ASTROCYTOMAS

8.1 Introduction

High-grade astrocytomas are the commonest type of brain tumour and are a major cause of morbidity and mortality in middle age and in the elderly. Long-term survival is rare.

Tumours of neuroepithelial origin account for more than half of all brain tumours, and more than 50% of these are high-grade astrocytomas. These tumours occur most commonly in the sixth to eighth decade of life and are slightly more common in males than females.[1–3] In Australia, there are more than 1300 primary brain tumours diagnosed each year.[4] In 2004, there were 1369 central nervous system (CNS) tumours, with 1080 deaths.

The prognosis for high-grade astrocytoma is very poor, with little change in survival since the 1980s[5,6] despite some incremental improvements in multimodality therapy.[7] The overall survival to two and five years is 36% and 28% respectively, and for the most malignant forms, average survival is generally less than 12 months, with only 3% of patients surviving to two years.[2] Patients eligible for chemo-radiotherapy have a better outlook with two-year survival of 26.5%.[7] Prognosis is worse for higher-grade histopathology, increasing age at diagnosis, poor performance status at presentation and possibly, residual disease after surgical resection.[9–17]

8.1.1 Causes and risk factors

There are currently few well-defined causes or known risk factors for high-grade astrocytoma, although both genetic and environmental factors have been suggested.[18,19] A minority of cases are associated with rare hereditary syndromes or therapeutic radiation. Of the genetic syndromes, Li-Fraumeni syndrome, a germline mutation of p53[20], neurofibromatosis types 1 and 2, Turcot syndrome, tuberous sclerosis and Ollier disease, account for a fraction of all cases.[19] Prior exposure to therapeutic doses of ionising radiation is known to be associated with later development of high-grade astrocytoma.[21,22] Exposure to environmental and dietary factors, and most recently, mobile telephone use, have all been suggested as risk factors and publicly debated. However, there is no clear evidence or consensus.[19,23–26] (For more information see *Chapter 1 Setting the scene*.)

8.1.2 Presentation and diagnosis

The clinical presentation of high-grade astrocytoma depends on the tumour location and rate of growth. They occur most commonly in the cerebral hemispheres and are less common in the posterior fossa and brainstem.[27–29] Presentation is most commonly with generalised symptoms, including headache and cognitive dysfunction.[30] Seizures are the second-most common presentation and the incidence of seizures is between 40% and 80% with an inverse relationship to tumour grade.[31,32] Focal neurological deficits are related to location of the lesion in the brain. Presentation with sudden symptoms due to haemorrhage is unusual[33–35] and symptom onset usually occurs over weeks to months.[27,28]

Initial investigation of high-grade astrocytoma is largely based on neuro-imaging. While imaging technology has advanced rapidly in recent decades, with increasingly accurate prediction of tumour type and extent, neuro-imaging cannot conclusively confirm the histological diagnosis or predict disease behaviour.[36,37] The modality of choice is contrast-enhanced magnetic resonance imaging (MRI), although computed tomography (CT) is often the first investigation performed due to cost and availability. The typical MRI appearance of high-grade astrocytoma is a hypo-intense or mixed density mass on T1-weighted images with heterogeneous or ring-like enhancement with contrast, but findings vary widely.[38–40] Signal abnormalities on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images show oedema surrounding the central tumour mass. Oedema may be

extensive, and also indicate infiltrating tumour cells, however tumour infiltration may extend beyond the imaging borders of the tumour.[41]

A number of newer neuro-imaging modalities are being investigated for more accurate prediction of histology, tumour recurrence, and treatment response, including magnetic resonance spectroscopy (MRS).[42–44] Diffusion-weighted MRI (DWI) and diffusion tensor imaging (DTI) may have the capacity to improve anatomic delineation of the tumour for treatment[45–51] and improve prediction of tumour grade[52] (*see Chapter 5 Imaging*).

8.1.3 Classification, histopathology and molecular biology

High-grade astrocytomas include WHO grade III (anaplastic astrocytoma [AA]) and grade IV (glioblastoma multiforme [GBM]) tumours.[53,54] Classification into grade has prognostic significance and is based on histological features. These divisions are descriptively useful but at times somewhat artificial. Immunohistochemical detection of antigens associated with cell division including Ki-67, may be used as an adjunct to determine a 'proliferative index' which correlates with histological grade and prognosis.[55–59]

Increasingly, molecular rather than histological descriptions and correlations are being sought for astrocytoma.[60,61] These are aimed at more accurately understanding tumour biology and predicting behaviour and treatment response.[62–65] It is becoming increasingly clear that histologically similar tumours may have distinct molecular phenotypes.[60,66,67] It is unclear whether these differences relate to the cellular origin or molecular genesis of the tumour or are a signature of different mechanisms of tumour progression.[68] Greater understanding of the biological, genetic and molecular characteristics of the central nervous system has led to a number of new hypotheses, including origin from stem cells or glial precursor cells and dedifferentiation from mature glial cells.[69–73]

Thus, recent advances in the genetics and molecular biology of cancer have led to a revolution in our understanding of high-grade astrocytoma. Simple classifications based on clinical, imaging and histopathological parameters are being superseded by increasingly complex descriptions of this heterogeneous group of tumours. This is best illustrated by the understanding that tumours with common histopathology actually comprise distinct molecular subtypes, typified by primary and secondary GBM (see below). Classification schemes have been largely based on the concept that astrocytomas show an inherent tendency to progression to a more malignant phenotype, and tumours have been morphologically categorised into the histopathological grading schemes described in chapter 6 *Diagnosis and pathology*.[68,74,75] Further investigation has shown that this progression is associated with the sequential acquisition of genetic alterations. These include initially, mutations in the *TP53* gene and homozygous deletions of the *p16* tumour suppressor genes and later, loss of heterozygosity (LOH) on chromosomes 10 and 19q and amplification of the epidermal growth factor receptor (EGFR). However, not all tumours have this molecular phenotype and two pathways are now defined.[76–78]

8.1.4 Primary and secondary GBM

Primary GBM appear to arise *de novo* with no precursor lesion and occur in older patients.[53,76,77] The most common abnormality found is amplification of EGFR[77,79], with a low rate of *TP53* gene mutation.[78] In addition, primary GBMs have a high frequency of loss of the long arm of chromosome 10.[77,79–81]

Secondary GBMs are thought to progress from lower-grade tumours by the pathway described above, and commonly occur in younger patients. The most common molecular abnormality in these tumours is mutation of the *TP53* gene[78,82], which is seen in 30–50% of astrocytomas of all grades.[57,83–85]

Both low- and high-grade astrocytomas are characterised by gains on chromosome 7.[86,87] The primary and secondary GBM pathways are not mutually exclusive and possibly interact. For instance, a GBM

with *TP53* mutations may also have a minority of cells with amplified EGFR, however, the *TP53* phenotype seems to inhibit widespread amplification of EGFR.[84,88] Thus, there is molecular heterogeneity within the two broad subtypes. A number of key pathways lead to the phenotype of malignant astrocytoma, with uncontrolled cell proliferation and survival, angiogenesis and invasion.

8.2 Management of high-grade gliomas

The management of high-grade gliomas may involve surgery for biopsy or debulking, radiotherapy, chemotherapy or a combination of treatments. In some circumstances treatment may not offer a benefit in survival or quality of life and should not be offered. Management decisions are complex and usually involve the patient, carer and several professional groups. The approach to decision making is discussed in *Chapter 2 Approach to the patient*.

8.2.1 Surgery

Tissue diagnosis in patients with high-grade astrocytoma suspected prior to commencing definitive treatment

There are no studies definitively demonstrating improved or similar outcome in patients with high-grade astrocytoma in whom a tissue diagnosis is obtained compared to those in whom there is diagnosis based on clinical or imaging criteria only. However, the following considerations are relevant.

A single retrospective study of 82 older patients (age 62–99) with suspected primary brain tumour on CT scan, showed that the 37 who were biopsied lived longer than those who were not (median survival 81 versus 47 days). However, there was strong selection bias for biopsy of younger and fitter patients, and treatments varied.[89]

Evaluations of CT, MRI and newer imaging techniques for accuracy in diagnosis of suspected high-grade astrocytoma, and differentiation from other tumours and non-tumour lesions, show variable sensitivity, specificity and positive and negative predictive value ranging from 50% to 100% depending on the study, which is not sufficient for a definitive diagnosis of tumour type or grade.[90–100] Most studies have compared imaging diagnosis with histological diagnosis, but vary in quality in terms of rigour of imaging quality control and experience of observers. However, overall, definitive diagnosis of lesion type and grade cannot be made on imaging alone.

There is no evidence to favour a particular biopsy technique, but observational studies have shown the mortality of biopsy to be 0–3% and morbidity 0–13%, with a diagnostic yield of 89–100%.[101–112] Retrospective comparisons favour image-guided over free hand biopsy but there are no randomised comparisons.[113,114]

Recommendations	Level	References
A tissue diagnosis should be obtained in all patients with a suspected high-grade astrocytoma before commencing definitive treatment.	III	115
Anti-neoplastic treatment should not be offered without a tissue diagnosis unless biopsy is considered too dangerous.	III	90–100

Effect of tumour resection, as compared with biopsy alone, on outcome for patients with high-grade astrocytoma

The evidence for an improvement in outcome with surgical resection for patients with high-grade astrocytoma, reviewed below, is scant and often of poor quality. Given that the majority of expert

opinion has favoured maximal tumour resection over the past three decades, additional reasons, other than improvement of survival, have often been given to support resection of tumour over biopsy.[116,117] These include:

- More accurate diagnosis, particularly of tumour grade, with the larger specimen of surgical resection as compared with the small specimens of biopsy, which are subject to sampling error.[116,118–120] *(see Chapter 6 Diagnosis and pathology)*
- Reduction of mass effect with improvement of symptoms and thus quality of life and better tolerance of adjuvant therapy and reduction of corticosteroid requirements.[121–123]
- Cytoreduction, which may have an oncological advantage and prolong survival sufficiently for adjuvant therapy to proceed. Additionally, surgery is the only cytoreductive therapy that not only kills, but also removes cells, which is of importance intracranially, and for which there is limited physiological capacity.
- Provision of tumour for research and analysis.

However, the quality of evidence that these aims are achieved is in general no better than for outcome in terms of survival, functional status or quality of life.

The effect of resection on outcome for patients with high-grade astrocytoma has been reviewed regularly, including recently by the UK National Institute for Health and Clinical Excellence in 2006.[124] They identified fourteen relevant studies: three systematic reviews, one randomised controlled trial and ten observational studies. A review of the subsequent literature revealed no relevant studies.

There is no high-quality evidence to suggest better outcomes from surgery over biopsy for patients with high-grade astrocytoma. A systematic review of randomised controlled trial evidence for The Cochrane Library[125] found one small trial that showed a modest but significant survival benefit following resection compared with biopsy in elderly patients. The study had significant methodological problems, particularly as only 23 of the 30 patients ultimately had an astrocytoma and it was underpowered.[126] This review concluded that resection could not really be supported. A similar review in 2004 suggested a statistically significant survival benefit for resection over biopsy but cautioned about the quality of the evidence, particularly selection bias.[127] An older review of non-randomised, largely retrospective studies reached the same conclusion but commented that there may be a subgroup of young patients who benefit from resection.[12]

Observational study evidence reaches no consensus.[11,128–130] The major methodological flaws of these retrospective studies are strong selection bias, incomplete data and quantification of extent of resection by inaccurate intra-operative assessment rather than post-operative imaging.[131] However, a number of these studies comparing biopsy with resection suggest a survival benefit for those undergoing surgical resection[132], including a recursive partitioning analysis of the literature for high-grade astrocytoma.[133] An analysis of patients in the Glioma Outcomes Project showed prolonged survival with tumour resection rather than biopsy. There was a strong selection bias for resection for younger patients with better performance status and unilateral, unifocal lesions. However, if patients aged over 65 years, those with a Karnofsky Performance Status (KPS) less than 70 and those with multifocal or bilateral tumours were excluded, the survival advantage persisted ($p = 0.0015$).[14]

In another analysis of 565 patients from the Glioma Outcomes Project data, GBM and AA were considered separately. For both there was significantly better survival for resection compared with biopsy. For AA this was 87 versus 52 weeks and for GBM 45 versus 21 weeks. This analysis was adjusted for age, KPS and multifocal or bilateral disease.[13]

Recommendation	Level	References
Patients with high-grade astrocytoma should have surgery for tumour resection if safe as this extends survival when compared to biopsy alone.	II	125,126

Effect of extent of tumour resection on outcome for patients with high-grade astrocytoma

As for surgical resection compared to biopsy alone discussed above, the evidence that extent of resection affects outcome is limited. A Canadian 2004 systematic review examined outcome after gross total tumour resection compared to subtotal or partial resection in malignant glioma.[127] They included five retrospective and five prospective studies, all of which suggested improved survival after gross total resection compared to subtotal or partial resection. There was likely to be significant selection bias, with younger, better performing patients being chosen for more extensive resection. However, this observational study evidence is suggestive of an advantage in terms of survival following gross total resection over partial resection.

Recommendation	Level	References
Patients with high-grade astrocytoma should have surgery for maximal tumour resection, aiming for gross macroscopic resection if safe, as this extends survival when compared to biopsy, subtotal or partial resection.	II	127

Effect of tumour resection on outcome in older patients (over 65 years) or those with poor performance status with high-grade astrocytoma

The evidence for improvement in outcome with resection in GBM patients with the poorest prognosis, that is, the elderly (age >65) and those with poor performance status (KPS <70) is scanty. In general, these patients are either excluded from studies or are included in the biopsy-only group, thus there is strong selection bias. However, the only randomised controlled trial of biopsy versus resection in GBM was conducted in elderly patients over the age of 65. This small trial showed a modest but significant survival benefit following resection compared with biopsy in elderly patients but had significant methodological problems.[126]

In older or poorly performing patients there may be significant concerns regarding fitness for surgery.

Recommendation	Level	References
Patients with high-grade astrocytoma who are over the age of 65 or have poor performance status should have surgery for tumour resection if they are fit for surgery, as this extends survival when compared to biopsy alone.	II	126

Effect of local chemotherapy (carmustine wafers) on survival for patients with high-grade astrocytoma

Systemic chemotherapy for brain tumours has been hampered by difficulty achieving adequate exposure to intracranial tumour with systemic administration without general toxicity. This effect is primarily due to the effectiveness of the blood–brain barrier. To overcome this problem, local delivery systems have been proposed, the most widely accepted being implantable chemotherapy wafers.[134,135] Since 1987, clinical studies have demonstrated a role for implantable carmustine polymer wafers

(Gliadel®) for the delivery of high local chemotherapy concentrations[136] to the tumour cavity after surgical resection.

Efficacy was first tested in recurrent high-grade glioma in patients who had already undergone maximal treatment, many with multiple craniotomies, radiotherapy and chemotherapy. In a 1995 prospective randomised phase III trial of 222 patients[137] there was an improvement in average survival from 23 weeks after repeat surgery to 31 weeks with carmustine wafer implantation. Mortality at six months for the GBM subgroup was decreased from 64% to 44%. In a subsequent case-control, retrospective study with 62 patients[138], no survival advantage was demonstrated.

Efficacy was then tested in newly diagnosed high-grade glioma. A 1997 randomised, prospective phase III trial with 32 patients[139] demonstrated an improvement in survival from a median of 40 weeks to 58 weeks after primary surgery, wafer implantation and radiotherapy as compared to surgery and radiotherapy alone. This study had relatively small numbers in both arms and had a mix of tumour types in the treatment arm and only GBM in the placebo arm. When only GBM was analysed against the placebo group, there was a significant survival advantage in the treatment arm but less than seen when mixed pathologies were included.

A larger prospective randomised multi-centre phase III trial by Westphal et al of 240 patients in 2002[140] demonstrated an improvement in median survival from 11.6 months to 13.9 months. This effect remained following adjustment for factors affecting prognosis and in subgroup analysis.[141] This study, however, had strict inclusion criteria and included younger neurologically-well patients who survived longer than average, even if they received placebo, than the usual cohort of patients with high-grade astrocytoma. A subsequent study suggested that only 25% of patients with an initial diagnosis of high-grade astrocytoma would be eligible for entry into that phase III trial and thus it was not reflective of all patients.[142]

Long-term follow up of the Westphal et al study[143] published in 2006 concluded that the survival benefit extended to two- and three-year endpoints in a statistically significant fashion. The GBM subgroup did not achieve statistical significance, however when integrated with the earlier phase III study by Valtonen[139], a statistically significant survival advantage was demonstrated.

There have been concerns about complications resulting from carmustine wafer implantation. Brem et al, in the 1995 placebo-controlled phase III prospective study of 222 patients, demonstrated no clinically important local or systemic side effects from the implanted 3.85% carmustine wafers.[144] Reported complications of seizures (19%), cerebral oedema (4%), poor wound healing (14%) and infection (4%) did not achieve statistical significance between the study and control groups. In the 1997 randomised prospective study of 32 patients at primary resection of high-grade astrocytoma[139], ten serious complications were identified in five of sixteen patients in the carmustine group compared with five serious complications in four patients of the control cohort. This study concluded that there was a higher incidence of complications in the carmustine wafer group. These findings were also observed in the retrospective study by Subach et al.[138] They found higher rates of CSF leak, wound dehiscence, meningitis and brain abscess in the carmustine wafer implantation group in recurrent GBM. Local complications are dependent on the carmustine dose in the wafer. Olivi[145] and Westphal et al[140] reported higher rates of both CSF leak and intracranial hypertension in the carmustine wafer treated patients with newly diagnosed high-grade astrocytoma. Another study of 46 patients treated with primary carmustine wafer implantation at surgery for newly diagnosed high-grade astrocytoma and subsequent standard external beam radiotherapy concluded that the radiotherapy is acutely well tolerated, however caution needs to be exercised during reduction of dexamethasone dose due to rebound cerebral oedema.[146] They also suggested difficulties in assessing tumour recurrence on MRI after wafer implantation due to local necrosis and advised caution, but this was not the finding of all authors.[147]

The National Institute for Health and Clinical Excellence (NICE) in the UK reviewed the evidence regarding carmustine wafers, reported in 2007. Based on FDA and manufacturer re-analysis of the

RCT data, they reported that carmustine wafers are effective for prolonging median survival but not progression-free survival in newly diagnosed high-grade astrocytoma. However, they determined that they should only be used in patients in whom 90% or more of the tumour had been resected.[148] This was based on a subgroup analysis showing this group to have the greatest survival benefit with carmustine wafers (median survival gain of 2.2 months over placebo), with no effect being seen in patients in whom lesser tumour resection was achieved. The difficulty of determining extent of resection intra-operatively was acknowledged.

The role of carmustine wafers in combination with concomitant temozolomide and radiotherapy, other systemic chemotherapy and radiotherapy is undergoing evaluation[149–151], but there is no evidence for efficacy or safety of concurrent carmustine and temozolomide. Carmustine wafers have not been compared directly with temozolomide as regards efficacy and safety (*see section 8.2.3 Chemotherapy).* The current Pharmaceutical Benefits Scheme provisions for carmustine wafers and temozolomide prevent the subsidy of both agents at diagnosis. The use of these agents should be planned by a multidisciplinary team.

Recommendation	Level	References
Patients with high-grade astrocytoma benefit from implantation of carmustine wafers at the time of surgical resection of tumour as they provide a modest survival benefit of 8 to 11 weeks.	I	139–141

Effect of resection of recurrent tumour on outcome for patients with high-grade astrocytoma

Despite recent advances that have led to some standardisation of initial treatment of high-grade astrocytoma, currently there is no standard for treatment of the inevitable recurrent tumour.

Recurrence may be defined as either radiological (asymptomatic) or clinical (symptomatic) evidence of new or enlarging tumour. This is often poorly defined in the literature discussed below, as is the timing of treatment, that is, whether symptomatic or radiological recurrence was treated. Practices varied widely but the main indication for a second operation was to postpone the onset of neurological symptoms and reduce the tumour bulk prior to further therapy. Thus many authors recommend re-operation in the asymptomatic or mildly symptomatic patient.[152,153] One study of 231 prospectively evaluated high-grade astrocytoma patients enrolled in other treatment trials reported that median survival of patients with asymptomatic radiological progression was significantly longer (42 weeks) than that of symptomatic patients (13 weeks).[154] Multivariate analysis revealed that more aggressive treatment of asymptomatic patients with surgery and second-line chemotherapy was the most important prognostic variable.

Differentiation of treatment effects–particularly radiation necrosis, but also the effects of chemotherapy–from tumour progression or recurrence is important and is discussed in *Chapter 5 Imaging*.

The stated indications for and aims of surgery in the management of recurrent high-grade astrocytoma are similar to those at the time of initial presentation.[155]

These include:

- Accurate histological diagnosis, particularly if the original tumour was of lower grade, but also to exclude radiation necrosis or to re-evaluate the tumour at the molecular level.
- Reduction of mass effect with improvement of symptoms, better tolerance of adjuvant therapy and reduction of corticosteroid requirements.

- Cytoreduction, which may have an oncological advantage and prolong survival sufficiently for adjuvant therapy to proceed. Additionally, surgery is the only cytoreductive therapy that not only kills but also removes cells, which is of importance intracranially, and for which there is limited physiological capacity.
- Provision of tumour for research and analysis.

A review of the modern English literature regarding surgery for recurrent high-grade astrocytoma yields 20 papers.[123,152,153,156–172] Overall, the quality of the evidence for an effect of resection on either length or quality of survival for recurrent high-grade astrocytoma is poor. The literature is characterised by strong selection bias, incomplete data and quantification of extent of resection by inaccurate surgeon estimate rather than post-operative imaging.[131] The selection bias is largely related to the choice of patients who are younger and fitter for surgery.

There has been no systematic review of the literature regarding efficacy of resection for recurrent high-grade astrocytoma. Of 17 studies that report survival with reoperation[152,153,156,157,159–166,168–170] four analysed prospectively collected data and the remainder were retrospective reviews. There are no randomised studies and a small number of low-grade tumours were often included in the study group. There was no significant difference in survival between the prospective and retrospective studies. The average age of the more than 750 patients in these studies was 50 years. This young cohort suggests selection bias for younger, and presumably fitter, patients for re-operation and many studies concluded there was a survival benefit, particularly for young fit patients. However, overall the average survival from diagnosis in re-operated GBM patients in these studies was 60.5 weeks, which is similar to that of best standard of care.[7] Based on the available literature, it cannot be concluded that surgery for recurrent high-grade astrocytoma increases survival. However, the consensus amongst authors is that, in selected patients, surgery may improve quality of survival.[156,161–166,168]

The risks of re-operation for recurrent high-grade astrocytoma are an important consideration in these often disabled and immunocompromised patients with limited survival, although not all studies include mortality and morbidity data. Reported mortality ranges between 0 and 17%. Eighteen of the studies described above reported mortality. The average mortality of more than 800 patients undergoing re-operation was 3%.[123,152,153,156,158–170,172] If two studies with very high mortality (17% and 11%)[161,172] are excluded, mortality was 1.6%. Twelve of these 18 reports also reported morbidity, with an average of 16%.[123,152,158,160,162–165,167,169,170,172] If the studies of Young et al[172], Fadul et al[123] and Chang et al[158] are excluded, morbidity was 7.6%. These three studies report morbidity rates of greater than 25%. Two of the three studies reporting high morbidity are prospective, thus the morbidity data may be more accurate and the reported morbidity of retrospective studies is likely to be an underestimate. These results are comparable to carefully documented, reported, generally accepted mortality and morbidity after craniotomy for any intra-axial tumour.[122]

Thus it may be concluded that surgery for recurrent high-grade astrocytoma carries minimal additional risk when compared to initial craniotomy. However, the reports of re-operation for recurrent high-grade astrocytoma favour young fit patients and probably under-report complications. One prospective study comparing first and second craniotomy for high-grade glioma found a higher rate of perioperative complications for second craniotomy, particularly neurological worsening and infection.[158] A higher infection risk after second craniotomy was also found in one other large prospective study.[173]

Recommendation	Level	References
Patients with recurrent high-grade astrocytoma, particularly younger, asymptomatic patients, may benefit from resection of tumour.	III	156,161–166,168

Minimum safety requirements for centres to perform surgery for patients with high-grade astrocytomas

Currently, neurosurgery for high-grade astrocytoma in Australia is performed in tertiary referral public hospitals and selected private hospital facilities with established neurosurgical staff and expertise.

In most instances, minimum safe requirements for neurosurgery in a particular centre are based on consensus and statutory regulations rather than evidence, which is rarely available. General considerations for the operating room include:

- Neurosurgery should be performed in a facility accredited through assessment by the Australian Council on Healthcare Standards (ACHS) (<www.achs.org.au>).
- Basic standards for operating rooms encompass numerous policy documents and regulations from Standards Australia (<www.standards.org.au>), State and Federal government, specialist medical colleges and the Australian College of Operating Room Nurses (ACORN).
- Provision of sterile equipment is an essential standard of neurosurgical care and is governed by Australian Standard AS/NZS 4187:2003 (<www.standards.org.au>). The maintenance of sterility of personnel and materials during surgical procedures is covered by ACORN Standards 2006 as are other standards of nursing roles, competency and continuing education (www.acorn.org au).
- NSW Department of Health Policy Directive TS10 'Standard Procedures for the Handling of Accountable Items in the Operating Suite and other Procedural Areas' (and other applicable State Government regulations) governs surgical counts during procedures (<www.health.gov.org.au/policies/>).
- The Australian and New Zealand College of Anaesthetists (ANZCA) recommends minimum standards with regards to provision of a safe anaesthetic in Technical Professional Document T1 'Recommendations on Minimum Facilities for Safe Administration of Anaesthesia in Operating Suites and Other Anaesthetising Locations – 2006'. This, and more than 50 other Professional Documents and recommendations, are available on the ANZCA website (<www.anzca.edu.au/resources/professional-documents>).

Recommendation	Level	References
Surgery for patients with high-grade astrocytomas should be conducted in accredited facilities complying with all relevant State, Federal, professional and educational policies, standards and guidelines.	III	156,161–166,168

In addition to a standard safe operating room, it would be generally agreed that centres conducting surgery for high-grade astrocytoma should have:

- On-site, 24-hour neuroradiology including CT, MRI and angiography, with experienced neuroradiology staff. Facilities should not be so physically removed from the main location of patient care so as to present an unreasonable danger to patients during transportation.
- An on-site intensive care unit (ICU) able to provide complex, comprehensive pre- and post-operative care. The Joint Faculty of Intensive Care Medicine of ANZCA gives recommendations for minimum standards for ICU and other policies (<www.jficm.anzca.edu.au/publications/policy/>). ICU staff with neuro-intensive care experience is recommended.

- A multidisciplinary team including, in particular, neurologists, radiation and medical oncologists, neuropathologists, neuroscience nurse specialist and allied health professionals and also general physicians for expertise and assistance in the peri-operative period. Specialty surgical services, including plastic and reconstructive surgery or otorhinolaryngology are also occasionally essential for high-grade astrocytoma surgery and should be available.

Recommendation	Level	References
Surgery for patients with high-grade astrocytomas should be conducted in a multidisciplinary environment with input from neuroradiology, intensive care, medical and radiation oncology, neuropathology, neurology, specialist surgery and nursing and allied health services.	III	156,161–166,168

Specialist neurosurgical operating room equipment, the availability of which would generally be considered mandatory for surgery for high-grade astrocytoma, although not necessarily used in every operation, would include:

- facilities to view imaging studies
- adjustable operating table with adaptation for rigid skull fixation
- operating microscope
- stereotactic equipment
- ultrasonic surgical aspiration device
- equipment for cortical mapping, including a cortical stimulator and somatosensory evoked potential equipment[174–176]

Recommendation	Level	References
Surgery for patients with high-grade astrocytomas should be conducted in a facility where an operating microscope, ultrasonic surgical aspirator and cortical mapping equipment are available.	III	156,161–166,168

More controversial has been the availability of emerging expensive technologies, particularly in smaller centres. These include frameless neuronavigation and intra-operative imaging, particularly MRI. Neuronavigation increases precision and reduces morbidity of surgery by better targeting surgery on the tumour and uses smaller openings in the skull.

The use of both framed and frameless neuronavigation is now common in centres conducting surgery for high-grade astrocytoma. Framed systems have historically achieved high spatial localisation and diagnostic yield. Frameless systems using MRI now offer accuracy comparable to framed systems.[177] A comprehensive review of the application and advantages of different systems is beyond the scope of this document, however, there is some evidence to recommend the use of frameless neuronavigation for all surgery for high-grade astrocytoma.

A retrospective review of 76 patients compared survival and extent of resection in surgery for high-grade glioma with and without neuronavigation.[178] Intra-operative neuronavigation was associated with significantly improved median survival (from 10 to 16 months) and number of patients with

gross total resection (from 38% to 64%). There was a non-significant reduction in neurological deterioration post-operatively in the neuronavigation group. In a large recent retrospective study[179] of 486 high-grade glioma patients undergoing surgery, improved outcomes were associated with the use of neuronavigation, although selection bias with use in younger patients with smaller lower-grade tumours who presented with a seizure and normal level of consciousness was evident. More patients were discharged home and hospital stay was shorter. Thus, age and grade accounted for the finding. Gross total resection was lower in the neuronavigation group.[179] A case-control prospective study of 104 patients with GBM in 2000[180] showed that intra-operative neuronavigation improved extent of resection (31% versus 19% gross total resection) with an associated improvement in mean survival (13 versus 11 months). However, a small prospective, randomised trial of neuronavigation in 45 patients with solitary contrast-enhancing tumours in whom neuronavigation was pre-operatively judged redundant showed no statistically significant difference in extent of resection or survival. The authors concluded that neuronavigation should not be considered routine.[181]

Recommendation	Level	References
Intra-operative frameless neuronavigation improves extent of resection and survival of patients with high-grade astrocytoma compared to unguided microsurgery, and its use is recommended.	III	178,180

Emerging technology

Intra-operative MRI (iMRI) has improved technically in recent years, allowing increasing use of this expensive technology in centres around the world. The chief intended advantage of this technique as opposed to intra-operative frameless neuronavigation is avoidance of inaccuracy resulting from intra-operative brain shift. Thus, extent of resection can be maximised and intra-operative complications minimised.[182–187] It is emerging and expensive technology and is not widely available at present.

One prospective study of 40 glioma patients (all grades) has shown an improvement in the gross total resection rate using iMRI following maximal resection using standard frameless neuronavigation. Despite the intent, 53% of patients did not have a gross total resection following standard neuronavigation but further surgery using iMRI achieved gross total resection in all.[188] Retrospective reviews have found similar findings with no increase in operative morbidity.[189,190] Despite the improvement in the extent of resection, a prospective case control study comparing iMRI and conventional surgery failed to show a survival advantage and operating times were increased by, on average, two hours.[191]

8.2.2 Radiotherapy

Effect of radiotherapy on survival for patients with high-grade astrocytoma

This discussion applies to high-grade astrocytoma in general since, particularly in earlier trials, the distinction between grade III and IV gliomas was unreliably and irregularly reported. The large majority are assumed to be high-grade astrocytomas (GBM and AA) although other malignant gliomas may have also been included. Where the distinction between GBM and AA was reported, the proportion of GBM to AA was typically about ten to one. Radiotherapy appears to benefit GBM and AA to a similar degree, but the absolute outcomes for AA are far more favourable. For example, the median survival after conventional radiotherapy for GBM in trial RTOG 7401- ECOG 1374 was 8.7 months compared with 27 months for AA.[192]

The first randomised trial to demonstrate conclusively that radiotherapy prolongs survival was the Brain Tumor Cooperative Group (BTCG) trial 69-01. From 1969 to 1972, this four-armed trial compared different treatment regimens following surgery for malignant glioma.[5] Three hundred and

three (303) patients were randomised to: supportive care including steroids; whole-brain radiotherapy; BCNU chemotherapy alone; BCNU chemotherapy with radiotherapy. The radiotherapy dose was 50–60Gy in 1.8–2.0Gy fractions.

The valid study group comprised 220 patients. The median survival of 14 weeks for the surgery-alone group was significantly different from that of 36 weeks for those who received radiotherapy.

The Scandinavian Glioblastoma Study Group showed a similar effect of radiotherapy in a controlled randomised trial starting in 1974.[193] After maximal debulking surgery, 118 patients with grade III and IV supratentorial astrocytoma were randomised to: supportive care; radiotherapy to the whole brain with a placebo drug; whole brain radiotherapy with bleomycin. The radiotherapy dose was 45Gy given in 1.8Gy daily fractions. For those receiving supportive care alone, the median survival of 5.2 months was significantly different from that of 11 months for those in the radiotherapy arms.

Other randomised trials have also shown this benefit for post-operative radiotherapy for high-grade astrocytomas.[6,194,195]

In a study by Shapiro et al, 33 patients were randomised to receive either intravenous carmustine and vincristine alone or the same drug regimen plus a radiation dose of 60Gy to the tumour bed.[196] This failed to show a significant survival benefit from radiotherapy though the patient numbers were small and the performance status of those in the non-radiotherapy arm was better.

Laperriere et al pooled the results of these trials to show a risk ratio for one-year mortality of 0.81 (95% confidence intervals 0.74–0.88) when post-operative radiotherapy is compared to no radiotherapy following surgery for malignant astrocytoma.[197]

Recommendation	Level	References
Patients with high-grade astrocytoma should have radiotherapy because this extends median survival times when compared to no radiotherapy.	I	5,6,194,195, 198

Effect of delay in initiation of radiotherapy on survival for patients with high-grade astrocytoma

Three studies[199–201] have examined the effect of waiting for radiotherapy for high-grade astrocytomas on outcome. Both studies were retrospective case series, but it would be difficult ethically to perform a prospective randomised study of the question. Do et al[200] reported on 182 grade III and IV astrocytomas treated with radiotherapy. They found that survival decreased by 2% per day for every day a patient waited for radiotherapy. Seven patients who were initially thought fit enough to be offered high-dose treatment died before radiotherapy started. These patients were excluded from the analysis so the true decrease in survival because of prolonged waiting times is likely to be greater than was estimated. Burnet[199] generated a model of the effects of waiting time from a cohort of 154 Grade IV astrocytomas treated to 60Gy and compared it with 129 Grade IV astrocytomas treated with radiotherapy alone as part of a randomised trial. They estimated that grade IV astrocytoma cells doubled every 24 days and that long-term survival decreased modestly with increasing delay to the start of radiotherapy.[201]

Recommendation	Level	References
Radiotherapy should start as soon as possible after a diagnosis of high-grade astrocytoma is established.	III	202,203

Optimal total radiation dose and fractionation regimen for patients with high-grade astrocytoma

A joint Radiation Therapy Oncology Group and Eastern Cooperative Oncology Group study (RTOG 7401, ECOG 1374) investigated the value of an increased radiation dose to the tumour bed for patients with high-grade gliomas.[192] From 1974 to 1979, 626 patients with high-grade gliomas underwent surgery and post-operative radiotherapy to a 'control' dose of 60Gy to the whole brain. Prior to radiotherapy they were randomised to one of the following options: no further treatment; a boost of 10Gy to the tumour plus a margin; BCNU chemotherapy given concurrently with the control radiotherapy then adjuvantly; Methyl-CCNU and DTIC chemotherapy given concurrently with the control radiotherapy and adjuvantly. There was no difference in local control or survival in those receiving the higher radiation dose. For GBM, the median survival times were 8.7 months for 60Gy and 7.7 months for 70Gy ($p > 0.05$). For AA, the survival times were 27 and 36 months respectively ($p>0.05$).

A United Kingdom Medical Research Council (MRC) study investigated two different radiotherapy doses in 474 adult patients with grade III or IV astrocytoma.[204] Using a two to one randomisation, 318 patients received 60Gy in 30 fractions and 146 received 45Gy in 20 fractions. The median survival of 12 months in the 60Gy group and nine months in the 45Gy group were statistically different ($P = 0.007$).

Walker et al examined the relationship between radiation dose and survival in 621 patients with malignant astrocytoma entered into BTCG trials 6601, 6901 and 7201 from 1966 to 1975.[205] Radiotherapy was given after definitive surgery. The median survivals for those receiving 50, 55 and 60Gy were 28, 36 and 42 weeks respectively. Median survival for the 60Gy group was 1.3 times that of the 50Gy group ($p=0.004$).

As a result of these early studies, 60Gy in 2Gy fractions has been accepted as the 'standard' radiotherapy dose and fractionation schedule for high-grade astrocytoma.

Recommendation	Level	References
The standard radiotherapy dose and fractionation schedule for patients with high-grade astrocytoma is 60Gy in 2Gy fractions and there is no evidence that higher doses improve outcome.	I	206-208

Effect of alternative radiotherapy fractionation regimens on outcome for patients with high-grade astrocytoma

The radiotherapy dose that can be delivered to a tumour is limited by normal tissue tolerance. The tolerance of normal brain using conventional 1.8–2Gy daily fractions is considered to be around 60Gy. For radiobiological reasons, if smaller fractional doses are used, normal late-reacting tissue tolerance is theoretically increased, while that of acute reacting tissue and tumour remains the same. This means that giving many small doses (hyperfractionation) may theoretically allow a higher, biologically effective dose to the tumour without increasing late normal tissue toxicity. Multiple smaller fractions may also reduce the tumour-protective effects of tissue hypoxia and increase the chance of irradiating the tumour during a more sensitive part of the cell cycle.

There have been two approaches to alternative fractionation schedules. Hyperfractionation (HF) is given at the rate of at least two small fractions per day, with several hours between fractions, but the overall treatment time is the same as for conventional fractionation. The total dose can be increased while maintaining an acceptable level of complications because smaller doses per fraction are better tolerated by neural tissue. Accelerated fractionation (AF) refers to a course of radiotherapy where more than one fraction (of conventional size) is given each day so that the overall treatment time is shorter than with conventional fractionation. The total radiation dose is usually reduced to keep acute

toxicity to an acceptable level. The rationale for acceleration is to minimise tumour cell repopulation, which is likely to increase as the overall duration of the course of treatment increases. Often altered fractionation schedules involve both HF and AF. The prime intent of these regimens is to benefit clinically from their radiobiological advantage. However, the shortened overall times of AF regimens may also be an advantage to patients with poor life expectancy.

Hyperfractionation

RTOG protocol 83-02 was a phase I/II study that investigated the use of HF partial brain radiotherapy after surgery for high-grade astrocytoma. Fractions of 1.2Gy twice daily to total doses of 64.8, 72, 76.8 or 81.6Gy were used to reducing partial brain fields. In the initial report, survival at the highest dose appeared worst, approaching statistical significance, while the survival and toxicity profile were most favourable at 72Gy.[209] However, the final report showed little difference between the treatment arms, and survivals were not significantly different from those in previous series where conventional fractionation had been used.[210]

This was followed up by RTOG 90-06, a phase III trial in which 712 patients with malignant gliomas were randomised to receive either a HF regimen of 72Gy given in twice daily fractions of 1.2Gy or a conventional regimen of 60Gy in 30 fractions. Initial and reduced partial brain fields were used and all received systemic carmustine on three consecutive days every eight weeks. There was no survival benefit from HF, with survival times of 13 and 11 months in the conventional and hyperfractionated arms respectively (P=0.15). Survivals times were significantly better in the conventional arm for all patients under 50 years of age and for all patients with GBM under 50.[211]

Prados et al[212] randomised 231 patients with GBM to post-operative partial brain radiotherapy using a conventional schedule of 59.4Gy in 1.8Gy daily fractions or a hyperfractionated schedule of 70.4Gy given in twice-daily fractions of 1.6Gy. Half the patients were also randomised to receive the polyamine inhibitor difluoromethylornithine (DFMO). There was no significant difference in survival between the conventional and the HF arms.

One study that showed a benefit of HF was that of Shin et al.[213] Forty-three patients were treated to 61.4Gy in 69 fractions over 4.5 weeks and 38 patients to conventional treatment of 58Gy in 30 fractions over six weeks. The median survival for the HF arm of 39 weeks was significantly higher than the 27 weeks for the conventional arm. This was a small study and the survival for the conventional arm was worse than in other published studies using conventional radiotherapy for high-grade astrocytoma. It has been noted that there was a higher percentage of GBM in the conventional arm.

Laperriere et al performed a pooled analysis for a systematic review on HF versus conventional radiotherapy for high-grade gliomas.[197] This demonstrated no significant benefit of HF. The risk ratio for 12-month mortality was 0.89, favouring HF, but the 95% confidence intervals ranged from 0.73 to 1.09.

Accelerated fractionation

Lutterbach et al treated 149 patients with GBM to 54Gy, using three 1.5Gy fractions per day.[214] The median survival of 8.8 months was not an improvement on conventional radiotherapy. EORTC Trial 22803 randomised 340 patients with high-grade astrocytoma to conventional radiotherapy of 60Gy in 30 daily fractions or AF of three fractions of 2Gy each day for five days, a two-week break, then repeat of the initial five-day schedule.[215] Those in the AF arm thus received 60Gy in four weeks instead of the conventional six weeks. A third arm randomised those in the AF arm to daily misonidazole. Median and two- and three-year survivals did not differ between the arms. To investigate whether the two-week gap during treatment contributed to the absence of benefit from AF, the EORTC Radiotherapy Co-operative Group performed a phase II dose escalation study up to 60Gy in 30 fractions in 12 days in GBM.[216] Again, median survival of 8.7 months for the group did not represent a survival advantage for these AF regimens.

The study reported by Werner-Wasik et al[210] quoted above in the discussion on HF included an AF arm of 1.6Gy twice daily to a total dose of 48 or 54.4Gy.[210] There were no survival differences between the treatment arms. Toxicity in the AF arm was low, suggesting scope for dose escalation.

Brada et al[217] performed a single-arm study of AF radiotherapy for malignant astrocytomas in 211 patients. The radiation schedule was 55Gy in 34 fractions delivered twice daily. Median survival of ten months was similar to that of conventional fractionation.

Recommendation	Level	References
For adjuvant radiotherapy for high-grade astrocytoma, conventional fractionation (single daily fractions of 2Gy) is recommended. There is no evidence that hyperfractionation and/or accelerated fractionation improves outcome.	I	218,219

Effect of delivery of a radiation boost by brachytherapy or stereotactic radiosurgery on survival for patients with high-grade astrocytoma

Brachytherapy and stereotactic radiosurgery both deliver highly conformal radiation to small volumes of tissue with rapid fall-off in dose outside the treated volume. Considerable dose inhomogeneity may exist within the irradiated volume. Brachytherapy is further characterised by the risk of bleeding and/or infection with catheter, seed or balloon placement and a variable dose rate that may affect the biological effects of treatment. Both treatment modalities have been used for salvage treatment following malignant astrocytoma progression[220,221] and as a means to escalate or boost the dose delivered with initial therapy (RTOG 93-05).[222]

Phase II data are available for brachytherapy as monotherapy for low-grade glioma[223] and as a boost for high-grade astrocytoma. Eligible patients are those fit enough to undergo surgery and tend to have smaller well-defined tumours that are accessible and do not cross the midline. The possibility of any treatment effect being confounded by patient selection has been raised, although some evidence exists for a treatment effect within each RTOG recursive partitioning analysis (RPA) class.[224]

Several studies employing a stereotactic boost are limited by the same caveats in terms of patient selection.[225] A median survival of 96 weeks (actuarial two-year survival of 45%) has been reported by Sarkaria.[226] This study and others also highlight the risk of focal dose escalation, with many patients requiring ongoing steroid support and an approximate 50% risk of developing radiation necrosis requiring re-operation.[227,228] Further surgical procedures may also confound any benefit seen by focal dose escalation. A recent systematic review[229] of conventional treatment and radiosurgery as a boost, concluded that no benefit was seen in terms of overall survival, local brain control or quality of life.

Recommendation	Level	References
Focal dose escalation with brachytherapy or stereotactic radiosurgery as part of initial radiotherapy for patients with high-grade astrocytoma does not improve outcome.	I	230

'Short course' radiotherapy compared to standard radiotherapy for patients with high-grade astrocytoma, particularly for those with the poorest prognosis

Full course radiotherapy with concurrent chemotherapy is the treatment of choice for fit patients with glioblastoma multiforme.[7] This section examines the role of short-course radiotherapy for patients with a poor prognosis.

Predictors of poor survival

There is concern that patients with poor prognosis may undergo long courses of radiotherapy for little benefit.[198] The factors that indicate a poor prognosis include patient age, performance status including degree of neurological impairment, no history of seizures and extent of surgery.[204] There have been several attempts to develop prognostic indices that categorise patients by their expected survival.

The MRC[204] in the UK divided 417 high-grade astrocytoma patients from the first MRC glioma trial into six groups (Table 8.1) that correlated with prognosis. Patients with a score of 0–15 had median survival of 51–53 weeks; those with a score of 16–25 had a median survival of 35–41 weeks and those with a score or 26–28 had a median survival of only 16–23 weeks. A six-week course of radiotherapy would occupy a significant proportion of the poorest groups' survival time.[231]

Other studies have attempted to apply the MRC prognostic scale to their own data. Latif et al[232] examined 236 patients treated between 1989 and 1995 and found good agreement. However, 79 patients were excluded because they would not have been eligible for MRC studies because of performance status or age. Year of referral was also significant, with patients treated in more recent years having a better survival probability. Akman et al[202] used a cohort of 119 patients to compare the MRC index with a new prognostic index that added tumour size, location and pre-operative and pre-radiotherapy neurological status to the MRC variables. The MRC groups had significantly different survival varying from 14 months for scores of 0–15 to eight months for scores of 26–33. Multivariate analysis showed age and tumour grade were significant. The sample size was small and reduced the power of the study.

Table 8.1 Medical Research Council (MRC) prognostic index

Factor	Category	Score
Age	<45	0
	45–59	6
	□60	12
Clinical performance status	0–1	0
	2	4
	3–4	8
Extent of surgery	Complete resection	0
	Partial resection	4
	Biopsy	8
History of seizures	3 months	0
	□3 months	5
	none	10

Source: MRC 1990[103]

The RTOG used recursive partitioning analysis (RPA) on the results of its trials to create a dataset of 1578 patients and identified six prognostic groups of high-grade astrocytoma patients (Table 8.2).[9] Prognostic factors included patient age, tumour grade, performance status, mental status, neurological function, extent of surgery and radiotherapy dose. The inclusion of *post hoc* factors such as radiotherapy dose reduces the validity and usefulness of the index to provide prospective assessment of prognosis.

Table 8.2 Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis prognostic groups

Class	Age	Grade	KPS	Symptom duration (months)	Mental status	Extent of surgery	Neuro deficit	RT dose
I	□50	AA			Normal			
II	>50	AA	70–100	>3				
III	<50	AA			Abnormal			
	<50	GBM	90–100					
IV	□50	GBM	<90					
	□50	AA	70–100	□3				
	□50	GBM	70–100			PR/CR	No	
V	□50	GBM	70–100			Biopsy	Yes	>54.4Gy
	□50	GBM	<70		Normal			
VI	□50	GBM	<70		Abnormal			
	□50	GBM	70–100			Biopsy		<54.4Gy

AA – Anaplastic astrocytoma (WHO Grade III); GBM – Glioblastoma Multiforme (WHO Grade IV); KPS – Karnofsky Performance Score; PR – partial resection; CR – complete resection; Neuro – neurological; RT – radiotherapy
Source: Curran et al[9]

The RTOG model was validated[203] on a dataset drawn from subsequent RTOG studies of about 1500 high-grade glioma patients. Median survival ranged from 59 months in Class I, to 4.6 months in Class VI (Table 8.3). The RTOG partitioning analysis classes accounted for about half of the variance in survival that was seen in the dataset.

Table 8.3 Survival of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes

Class	Median survival (months)	Two-year survival (%)
I	59	76
II	37	68
III	18	35
IV	11	15
V	9	6
VI	5	4

Source: Scott et al[203]

The MRC and RTOG prognostic systems are complex, methodologically flawed and of limited generalisability because they were derived from patients selected as fit enough to enter clinical trials. They are also based on old studies from the pre-concurrent chemotherapy era and there is some evidence of improvements in survival over recent years.[206,232] Recently, a simpler prognostic system has been proposed.[207] Patient age and neurological performance status (Table 8.4) were used to define a favourable and an unfavourable group (Table 8.5).

Table 8.4 Neurological performance status

Category	Neurological function
0	No neurological deficit
1	Some neurological deficit but fit for work
2	Neurological deficit causing moderate functional impairment
3	Neurological deficit causing major functional impairment
4	No useful function, inability to make conscious responses

Source: Gupta and Sarin[207]

Table 8.5 Simplified prognostic grouping

Category	Age	Neurological performance status
Favourable	□50 years	0 to 2
	>50 years	0 to 1
Unfavourable	□50 years	3 or 4
	>50 years	2 to 4

Source: Gupta and Sarin[207]

One may conclude from the plethora of prognostic indices that poorer outcome can be predicted by older patient age, higher tumour grade, and poorer neurological function. However, none of these variables is predictive in isolation; all of the attempts to generate prognostic indices recognise the complex interplay of the predictive factors. Good performance status is more predictive of outcome than age.[208] Clinical judgement must weigh up the combination of factors and consider the patient and their family's wishes in considering management options for high-grade astrocytomas.

Short course radiotherapy

Many single-arm studies[206,208,218,219,231,233–239] have reported the results of short courses of radiotherapy on selected and unselected patients with high-grade astrocytomas. Selection criteria include age >60, age>70, poor performance status or poor prognosis MRC or RTOG group. Most studies have examined total doses of 30–40Gy in 3Gy fractions (range 28Gy in four fractions to 51Gy in 17 fractions). Median survival ranged from four to 13 months. Comparisons with historical controls have shown similar outcomes to higher-dose regimens but all studies have been small and lack power. Age alone was not always predictive of poor outcome. Bauman[206] reported survival benefit from high-dose radiotherapy in elderly patients with KPS>50 when compared to short-course radiotherapy. Age did not predict outcome in patients >70 years[208] after adjustment for RTOG prognostic classes. Some studies[218,231,233] reported patients who survived one year or more indicating heterogeneity of tumour response and the difficulty of reliably determining prognosis.

Four randomised controlled trials have compared radiotherapy dose regimens. The MRC[204] randomised 474 adults with grade III or IV astrocytoma to receive 45Gy in 20 fractions or 60Gy in 30 fractions. Patients were aged between 18 and 70 years and their neurological function was 'not so seriously impaired as to make radiotherapy undesirable'. Survival was statistically significantly better in the 60Gy arm, with a median survival of 12 months, compared with nine months in the 45Gy arm. A significant improvement in survival with the higher dose was still apparent in the poorest prognostic group, although the overall survival was worse.

Roa et al[240] reported a trial of 100 poor-prognosis patients randomised to receive 60Gy in 30 fractions or 40Gy in 15 fractions. Patients were ≥60 years old and had GBM and Karnofsky Performance Status

(KPS) >50. The study intended to recruit 200 patients but closed after five years when 100 patients had been accrued. Median survival, health-related quality of life and KPS in each treatment arm were not statistically different. Another small, randomised trial of short-course radiotherapy for poor prognosis high-grade glioma patients was reported by Phillips.[241] Between 1990 and 1996, 69 patients were randomised to 60Gy in 30 fractions or 35Gy in ten fractions. All high-grade astrocytoma patients were eligible except for those ≤45 years with ECOG performance status 0–2. Median survival was 10.3 months in the 60Gy arm and 8.7 months in the 35Gy arm, but this difference was not statistically significant because of the small numbers involved.

A recent randomised study compared 50Gy with best supportive care in patients with GBM who were 70 years or older.[242] Eighty-five patients were randomised and the study was stopped at the first interim analysis because of the significant survival benefit in the treatment arm (29 weeks versus 17 weeks, p= 0.002). Radiotherapy halved the hazard of dying. There were no severe adverse events related to radiotherapy.

Conclusion

There are groups of patients with high-grade astrocytoma who are unlikely to live for long after their presentation. The predictors are older age, higher-grade and poorer performance status. The extreme cases are clear-cut; moribund patients should not be offered radiotherapy because they are very unlikely to benefit. Very fit patients, regardless of age, should be offered radiotherapy because it may give them a survival benefit. Patients in the middle ground with older age and mild deficits or younger age and more severe deficits are much harder to advise. Some will get a survival benefit from radiotherapy, but the proportion that benefit and the degree of benefit is likely to be reduced.

The evidence base for short-course low-dose radiotherapy is weak. The single institution, single-arm studies are very heterogeneous and the only conclusion that can be drawn from them is that short courses are tolerated acutely. One randomised trial confined to patients 70 years and older showed a significant survival benefit for high-dose radiotherapy when compared with no treatment. The MRC study is the largest study and showed a benefit for the higher dose even in poor prognosis patients. The two randomised trials that specifically examined poor prognosis patients were both very small, accrued slowly and were stopped prematurely because of poor accrual.

Research is needed to determine the role of temozolomide in the poor-prognosis patient group. Temozolomide prolongs survival when given with a full course of radiotherapy.[7] It may be valuable in poor-prognosis patients either alone as a substitute for radiotherapy or in combination with radiotherapy.

Recommendation	Level	References
There is insufficient evidence to recommend short-course radiotherapy.	II	104

Optimal total radiotherapy target volume for patients with high-grade astrocytoma

Randomised controlled trials originally demonstrated an improvement in overall survival when radiotherapy was delivered to the whole brain (WBRT) following surgical resection of high-grade astrocytoma.[5,6,194]

Subsequently, whole versus partial brain irradiation for high-grade astrocytoma was examined by Shapiro et al.[243] In Trial 8001 of the Brain Tumor Cooperative Group, 571 patients with malignant astrocytoma were treated with radiotherapy plus one of three randomly allocated chemotherapy schedules. In the earlier part of the trial, all patients received 60Gy WBRT. However, in the later part they were randomised to receive this same schedule or 43Gy to the whole brain, with a boost to the

tumour volume of a further 17Gy. There was no statistically significant difference in survival times associated with the two radiotherapy schedules. This showed that partial brain radiotherapy can be use, at least for part of the course, thereby potentially reducing neurotoxicity. Furthermore, because 43Gy is unlikely to sterilise microscopic tumour deposits, it is unlikely that inclusion of the WBRT for part of the treatment would confer any advantage over merely treating the tumour plus a margin for the entire course.

A review of recurrence patterns by Wallner et al also supports the use of partial rather than WBRT.[171] They studied the recurrence patterns in 34 patients who had previously received surgery and radiotherapy for high-grade astrocytoma. In only two of 34 patients were recurrences multifocal and 78% (25/32) of the unifocal recurrences were within 2cm of the original pre-surgical tumour margin.

A further report by Gaspar et al also documents the failure patterns in 53 patients with recurrent tumour after previous radiotherapy for high-grade astrocytoma.[244] Ninety six percent of these recurrences were in the brain alone and of those all were within 4cm of the enhancing volume as defined on the pre-operative CT scan.

Halperin et al reported an autopsy series of unirradiated (or minimally irradiated) patients with GBM for whom *ante mortem* CT images were available.[245] Hypothetical radiotherapy fields were designed based on the imaging. The autopsy correlation showed that, in all cases, all detected tumour cells would have been included in radiotherapy fields, which extended 4cm beyond the peritumoural oedema.

These data indicate that as the advent of CT and MRI scanning has allowed definition of the tumour extent, radiotherapy to tumour plus an adequate margin should be used for high-grade astrocytoma, as WBRT is associated with greater neurotoxicity with no improvement in outcome.

Recommendation	Level	References
For patients with high-grade astrocytoma, post-operative radiotherapy fields should include the tumour bed with a margin rather than the whole brain.	II	246,247

Defining target volumes in radiotherapy for patients with high-grade astrocytoma

As described above, reduction of the radiation field to cover the radiologically apparent tumour (so-called involved field radiotherapy [IFRT]) was proposed when analysis of failure patterns following WBRT demonstrated 70–90% of recurrences occurred within 2–3cm of the original tumour.[171,244,248,249] In addition, sparing of brain tissue would potentially decrease the likelihood of neurotoxicity occurring as a late sequelae of therapy.

WBRT and IFRT have not been prospectively compared with respect to local control, overall survival, neurological and neuropsychological outcomes.

Retrospective studies demonstrate equivalent recurrence patterns[250–253], local control and a trend towards better neuropsychological outcomes[230] in those receiving IFRT compared to WBRT.

Delineation of an appropriate target volume in IFRT of high-grade astrocytoma is controversial because of the discrepancy between real tumour invasion and that estimated by CT and MRI.[254] Target volume definition is assisted by studies correlating CT and MRI with pathological findings in untreated patients and studies correlating CT and MRI with patterns of failure following radiation therapy.

These studies demonstrate that the central low-density tumour area on CT and low intensity area on T1-weighted MRI corresponds histologically with necrosis, while the surrounding contrast-enhancing

ring on CT or high-signal intensity region on T1-weighted MRI corresponds to a rim of viable tumour cells. The area surrounding this rim, which appears hypodense on CT and hyperintense on T2-weighted MRI, corresponds to oedematous brain tissue with infiltrating viable tumour cells.[255,256] These cells extend throughout a 3cm margin from the border of the necrotic centre defined on CT scans[245,248,255,257] and throughout the hyperintense regions on T2-weighted MRI.[256] Isolated tumour cells beyond these areas have been found in between 25 and 33% of patients.[258,259]

Similarly, pattern of failure analysis demonstrates that, irrespective of whether WBRT or IFRT is employed, 70–90% of recurrences occur within 2–3cm of the original tumour site.[171,244,248,249] Thus failure to control the central zone of tumour remains the predominant problem in the radiotherapeutic management of high-grade astrocytoma.

Based on the available literature, the following option for target volume delineation in high-grade astrocytoma has been suggested.[260] The Gross Tumour Volume (GTV) is defined by the contrast-enhanced zone on CT or MRI. The Clinical Target Volume (CTV) encompasses the GTV and the high-signal area on T2-weighted MRI or the hypodense perifocal zone on CT. The Planning Target Volume (PTV) is defined by the CTV plus a 5mm margin in all directions. Some authors suggest a two-phase technique if the CTV is very large (>250cm^3), with the boost dose of 10–20Gy delivered to a target volume defined by the GTV plus a 1cm margin.[261]

Ideally, target volume delineation should utilise both CT and MRI. The extent of tumour infiltration or oedema is more clearly defined on T2-weighted MRI than on examination of hypodense areas on CT.[256] Quantitative assessments of the contribution of CT and MRI to composite target volumes demonstrate that while 50% of the composite CTV is apparent on both MRI and CT, MRI and CT contribute independently to the volume, with 28% of the composite CTV apparent on MRI only and 21% apparent on CT only.[262] As tumour volumes independently apparent on CT and MRI have equal validity, both imaging modalities should be used in radiation therapy treatment planning for high-grade astrocytoma.

The clinical utility of new imaging modalities (such as PET and MR spectroscopy) in treatment planning of high-grade astrocytomas is still under investigation.

Recommendations	Level	References
For radiotherapy for high-grade astrocytoma, involved field radiotherapy provides equivalent rates of local control and recurrence patterns to whole-brain radiotherapy.	III	230,251–253,263
The treatment volume or planning target volume (PTV) is defined as: • clinical target volume (CTV) + 5mm • CTV = Gross tumour volume (GTV) + high-signal area on T2-weighted MRI or perifocal hypodense zone on CT • GTV = contrast-enhancing area on CT or T1-weighted MRI	III	255
Both CT and MRI should be used for target volume delineation.	III	256,262

Optimal method for differentiating radiation necrosis from tumour progression

Radiation necrosis may lead to neurological dysfunction, oedema and mass effect. The tolerance dose defined as the 5% complication rate in five years (TD5/5) for partial brain irradiation is about 60 + 10Gy with conventional radiation.[264] In actuarial terms, the incidence of biopsy-proven radiation necrosis increases with time and may be estimated at 5%, 9% and 13% at 12, 24 and 36 months respectively, with a mean latent interval of 11.6 months. Radiation necrosis is rarely seen below 45Gy

in 20 fractions (Biological Equivalent Dose of 48Gy in 2Gy fractions) and chemotherapy may be associated with a fivefold increased incidence compared to radiation alone.[265] An increased risk has been linked to histology, with patients with primary brain tumours more likely to develop necrosis using focal irradiation than patients with metastases.[266]

The significance of radiation necrosis lies with the difficulty in distinguishing from progressive disease. Various strategies, including CT scan and MRI[267], including magnetic resonance spectroscopy and diffusion weighted imaging[268], thallium SPECT and PET have all been used with variable success. Changes seen in imaging may evolve over time and less severe injuries particularly affecting white matter are frequently demonstrated. PET scanning has been associated with a sensitivity of 80–90% and a specificity of 50–90%.[269] Histology remains the gold standard for diagnosis, although the subsequent effect on treatment decisions is less clear.[270]

A number of therapies have been suggested for management. Dexamethasone has been found to be of most benefit in the early development of radiation injury.[271] Steroid requirements were reduced in an early report detailing vascular endothelial growth factor (VEGF) inhibition using bevacizumab.[272] Hyperbaric oxygen therapy has been employed with limited data suggesting a possible role in children.[273] Surgery may be required to treat[274] symptomatic mass effect or to avoid the complications of long-term steroid usage.

Recommendation	Level	References
Histopathology remains the gold standard for diagnosis of radiation necrosis.	III	271

8.2.3 Chemotherapy

In the more recent chemotherapy trials, AA and GBM are more frequently reported separately. Thus these tumours will be considered separately unless otherwise stated.

Outcomes of adjuvant chemotherapy after surgery and radiotherapy in patients with glioblastoma multiforme

A literature search revealed three meta-analyses with similar conclusions. Two earlier meta-analyses, published in 1989 and 1993, have been criticised for methodological flaws. The meta-analysis published by the Glioma Meta-analysis Trialists Group in 2002[275] identified 3004 patients in 12 randomised trials and used individual patient data (Class IA). In this meta-analysis, 62% of the patients had GBM. This meta-analysis showed a reduction in the hazard ratio (HR) for death of 0.85 (95% confidence interval (CI) 0.78–0.92). This is equivalent to an improvement in one-year survival of 6% (95% CI 3%–9%), from 35% to 41%. Mean progression-free survival increased by 1.5 months (95% CI (0.5–2.5 months), from six months to 7.5 months. Few of the trials incorporated quality of life data and multiple drugs were used and thus choice of drug is not specified. Review of the literature since this meta-analysis was performed did not reveal any relevant trials.

Key point:

Adjuvant chemotherapy after surgery and radiotherapy provides modest improvement in progression-free survival and overall survival for patients with GBM.

Recommendation	Level	References
Adjuvant chemotherapy alone has been supplanted by concurrent chemo-radiotherapy followed by adjuvant chemotherapy and is thus not currently recommended.	II	7

Outcomes of adjuvant chemotherapy after surgery and radiotherapy in patients with anaplastic astrocytoma

A pre-temozolomide literature review revealed the same three meta-analyses identified for GBM. The proportion of AA in the Glioma Meta-analysis Trialists Group was 24%.[275] Subgroup analysis of the data showed a similar benefit for AA from the addition of chemotherapy, and an absolute increase in survival at one year of 5%, from 58% to 63%, and an increase in survival at two years of 6%, from a baseline of 31% to 37%. Quality of life was not examined.

Literature review of studies completed since this meta-analysis showed no further contributing studies. There is no quality of life data and the choice of drug is not specified.

Recommendation	Level	References
Adjuvant chemotherapy after surgery and radiotherapy improves survival and is recommended for patients with anaplastic astrocytoma (AA).	I	275

Outcomes of concurrent radiotherapy and chemotherapy followed by chemotherapy (Stupp protocol) in patients with glioblastoma multiforme

The study by Stupp et al[7] is the only randomised study that has addressed this question. The study compared post-operative radiotherapy (60Gy) to post-operative concurrent chemotherapy (temozolomide 75mg/m^2 daily) and radiotherapy (60Gy) followed by six months of temozolomide (150–200mg/m^2 days 1–5 every 28 days for six cycles). Overall, there was a significant improvement in median survival (12.1 months versus 14.6 months) and two-year survival (10.4% versus 26.5%) in favour of the chemotherapy arm. There was minimal additional toxicity in the chemotherapy arm.

Recommendation	Level	References
Concurrent radiotherapy and chemotherapy followed by adjuvant chemotherapy provides a significant improvement in median and two-year survival in patients with GBM and is recommended.	II	7

Outcomes of concurrent radiotherapy and chemotherapy followed by chemotherapy (Stupp protocol) in patients with anaplastic astrocytoma

The study by Stupp et al[7] did not include patients with AA. There are no data to recommend this therapy in these patients and neurological toxicity of combined radiotherapy and chemotherapy in longer-surviving patients has not been assessed

Recommendation	Level	References
There are no data regarding either safety or efficacy of concurrent radiotherapy and chemotherapy followed by chemotherapy in patients with anaplastic astrocytoma and the regimen is not recommended.		7

Outcomes of concurrent radiotherapy and chemotherapy followed by chemotherapy (Stupp protocol) in poor performance status patients (ECOG 3-4) with glioblastoma multiforme or anaplastic astrocytoma

The study by Stupp et al[7] did not include patients with performance status of 3 or 4. There are no data to recommend this therapy in these patients.

Recommendation	Level	References
There are no data regarding concurrent radiotherapy and chemotherapy followed by chemotherapy in patients with performance status 3 or 4 and glioblastoma multiforme or anaplastic astrocytoma and the regimen is not recommended.		7

Outcomes of concurrent chemotherapy and radiotherapy followed by chemotherapy (Stupp protocol) in elderly patients (over 70 years) with high-grade astrocytoma

The median age of patients on the landmark clinical trial of adjuvant chemoradiotherapy followed by adjuvant temozolomide for GBM was 56 years, with an age range of 18 to 71 years.[7] Patients over 70 years were excluded from the study. Hence, there is no evidence to confirm or refute that patients over the age of 70 benefit from this regimen.

A small reported case series treated 22 GBM patients over 65 years of age with adjuvant temozolomide 150 mg/m^2 for five of every 28 days with a mean of 4.9 cycles per patient following surgery and radiotherapy.[276] Treatment was adequately tolerated and survival was significantly better than retrospective comparators receiving surgery and radiotherapy only (median survival 14.9 months). No concurrent combined treatment (radiotherapy with temozolomide) was given in this series.

Recommendation	Level	References
As there are insufficient data to make a recommendation for management with concurrent adjuvant radiotherapy and chemotherapy followed by chemotherapy in patients over 70 with glioblastoma multiforme or anaplastic astrocytoma, treatment decisions should be made on an individual basis.		277

Outcomes of chemotherapy alone, without radiotherapy in elderly patients (aged over 70 years) with high-grade astrocytoma

A single-centre phase II study has examined the efficacy of temozolomide without radiotherapy in elderly patients.[278] Thirty-two patients over the age of 70 with histologically confirmed GBM and AA and an ECOG PS of 2 or better were treated with post-operative temozolomide 150–200 mg/m^2/day x 5 q28 days until disease progression. No radiotherapy was allowed on-study. The majority of patients (n=25) had only a biopsy prior to chemotherapy. A median of four cycles was administered, with a

median overall survival from diagnosis of 6.4 months and median progression-free survival of five months. Nine patients (31%) had an objective partial response, and a further 12 patients (41%) had stable disease as their best response. Fifty percent of patients benefited in terms of an improvement in KPS, reduction in corticosteroid dose, and/or improvement in Mini Mental State Examination (MMSE) scores. Safety and tolerability were confirmed in this elderly population (median age 75) with no treatment-related deaths.

Recommendation	Level	References
Post-operative adjuvant temozolomide without radiotherapy is safe and tolerable in patients over age 70 with good performance status. Comparison of outcome with other regimens has not been made. Treatment decisions should be made on a case-by-case basis.	IV	278

Outcomes of chemotherapy alone, without radiotherapy in poor-performance status patients (PS3/4) with high-grade astrocytoma

Radiotherapy or concurrent radiotherapy and chemotherapy for high-grade astrocytoma is of less benefit to patients with a poor-performance status.[7,277] Chemotherapy, particularly well-tolerated temozolomide, given without radiotherapy may be less toxic and effective as the initial post-operative adjuvant therapy in these patients. However, there are no reports of clinical trials or retrospective reviews that directly address this question. Non-randomised data are available on the use of temozolomide without radiation as initial therapy in elderly patients with GBM. A retrospective review of 86 consecutive patients identified 32 given temozolomide as an alternative to radiation.[279] Temozolomide was well tolerated and survival was not different between radiotherapy and chemotherapy-alone groups. The KPS was ≤ 70 in 60 patients and a low KPS predicted for poor outcome. However, among patients with a poor performance status, no comparison of outcomes by treatment modality (radiotherapy or temozolomide) was reported.

Recommendation	Level	References
There are no data regarding chemotherapy without radiotherapy for patients with high-grade astrocytoma and poor performance status and chemotherapy alone is not recommended as an alternative to radiotherapy.		277

Outcomes of chemotherapy in patients with recurrent high-grade astrocytoma

Many patients with recurrent high-grade astrocytomas are offered chemotherapy; however, the evidence supporting its use is derived almost exclusively from single-arm phase II studies. Interpretation of the results of these studies is complicated by a variety of study design factors.

The published clinical data clearly identify chemotherapeutic drugs and regimens that possess modest activity in recurrent high-grade astrocytoma. Active single agents include temozolomide, carmustine, lomustine, cyclophosphamide, carboplatin, liposomal doxorubicin, oral etoposide and irinotecan.[280–290]

In AA, these have resulted in overall response rate (ORR) of 22–34%, six-month progression-free survival (PFS-6) of 30–49%, median time to progression (TTP) of 4–5.5 months and median overall survival (OS) of 8–14 months.

The results in GBM are consistently worse, with ORR of 5–20%, PFS-6 of 8–21%, median TTP of 3–4 months and median OS of 5–7.5 months. Few studies included health-related quality-of-life

evaluations, but these measures showed improvement (or failure to decline) in association with objective responses to chemotherapy or progression-free status when reported.[281,289,290] A randomised phase II comparison of temozolomide with procarbazine showed a statistically significant difference in PFS-6 and median PFS favouring temozolomide, although the median PFS was only prolonged by one month.[289]

Toxicity profiles of these agents are variable and the overall excellent tolerability of temozolomide has contributed to its emergence as the drug of choice for high-grade astrocytoma, despite a lack of convincing evidence of superior anti-tumour activity. Prolonged schedules (such as seven-days on/seven days off; three weeks on/one week off) have not, however, demonstrated clearly superior efficacy in phase II clinical trials.[291,292]

A number of multi-agent chemotherapy regimens have shown activity in relapsed high-grade astrocytoma. In phase II studies of predominantly or exclusively GBM patients, chemotherapy combinations have resulted in overall response rate (ORR) of 11–30%, PFS-6 of 29–34%, median TTP of 3–4 months and median OS of 8–12 months.[246,293–297] Randomised trials comparing single drugs with combination chemotherapy have not been reported in recurrent disease. The decision on whether to use a multi-agent chemotherapy regimen should also take into account the potentially greater toxicity of combinations compared to single agents.

The standard of care for initial therapy of GBM has now become post-operative radiotherapy with concurrent and adjuvant temozolomide, following publication of the phase III trial showing a survival benefit for this approach compared to radiation alone.[7] Since most trials of chemotherapy in relapsed disease were performed prior to the widespread use of temozolomide in initial therapy, the relevance of the available data to treatment decisions for current patients with relapsed high-grade astrocytoma is increasingly difficult to evaluate. Nonetheless, a few studies have enrolled only temozolomide failures and shown activity with the investigational chemotherapy.[283,294]

Anti-angiogenic agents have been combined with chemotherapy treatment of recurrent high-grade astrocytomas. The combination of thalidomide with carmustine was evaluated in a phase II trial which recruited predominantly relapsed GBM patients exposed to prior chemotherapy.[247] The combination showed modest activity, but potentially contributed to a high rate of thromboembolic complications (12/40 patients developed deep vein thrombosis or pulmonary embolism). A recent report of the combination of irinotecan with bevacizumab (an anti-vascular endothelial growth factor monoclonal antibody) revealed a very high ORR of 63% among 32 patients with recurrent high-grade astrocytoma (predominantly GBM) in whom initial radiation and concurrent temozolomide had failed.[298] Treatment was well tolerated and resulted in a PFS-6 of 38%. This combination is promising, but requires further evaluation.

This patient group is ideal for consideration of participation in clinical trials of new agents. (*See Chapter 3 Clinical trials.)*

Recommendation	Level	References
Chemotherapy has modest activity in recurrent high-grade astrocytoma. A decision on its use should be made after discussion of risks and benefits, and consideration of other therapeutic options, but is generally recommended for good performance patients.	III	290–292

Optimum duration of temozolomide treatment in patients with recurrent high-grade astrocytoma

A literature review found 16 trials examining the use of temozolomide in recurrent GBM, and 14 for AA, none of which were relevant to the question. There is no evidence to guide clinicians as to how

long to treat patients with recurrent disease with temozolomide, and the decision should be individualised, with emphasis on symptoms, comorbidities, toxicity of treatment, imaging, and patient preference.

Key point:

- The optimal duration of temozolomide treatment in patients with recurrent high-grade astrocytoma is not yet defined.

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9 OLIGODENDROGLIOMAS

9.1 Introduction

In recent years the histological criteria for oligodendrogliomas have been better defined. The rate of diagnosis is increasing and may now make up to 25% of newly diagnosed malignant glioma.[1] This may be because of the improved prognosis, and response to therapy, particularly chemotherapy. The incidence appears to be similar across races.[2] Oligodendroglioma grade II tumours commonly present in the late 30s and early 40s[2,3], and anaplastic oligodendroglioma (grade III) tumours present a decade later and have a male preponderance of 1.5–2:1. The most common presenting symptom is partial seizure (up to 70%). Fifty to sixty percent of tumours are located in the frontal lobe although they may occur anywhere within the white matter.[4] However, the diagnosis of oligodendroglioma has also shown the limitations of pathology, and has been one of the early pointers to the importance of biological markers in directing therapy.

9.2 Problems with diagnosis

The definition of oligodendroglial tumours is fraught with difficulty. 'Pure' oligodendrogliomas (OG) have a classic appearance, but as they become more aggressive they dedifferentiate and become less typical. Mixed oligoastrocytoma (OA) is even more difficult to precisely delineate.

9.2.1 Radiologic appearance

Oligodendroglial tumours, particularly those of lower grade, tend to involve the cerebral cortex and subcortical white matter. Classically, they have been characterised by calcification.

More recently, there have been a number of imaging signatures comparing tumours that have deletions of 1p and 19q (1p-/19q-) to those oligodendroglial tumours without such losses. In summary, 1p-/19q- tumours are characterised by frontal lobe involvement (compared to temporal lobe in tumours with intact alleles), more commonly cross the midline, an indistinct border (versus a sharply defined edge), the presence of calcification or its MRI equivalent of paramagnetic changes.[5] As well, imaging with Thallium SPECT and FDG PET may show increased activity above that expected for a low grade glioma in oligodendroglial tumours with 1p/19q allelic loss.[6,7] Cerebral blood volume (CBV) maps have been used to assess the grade of glioma by measuring vascular density. There is generally a good correlation with grade except for low-grade oligodendrogliomas in which the CBV is also increased. This may be explained by the known 'chicken wire' vascular pattern characteristic of classic oligodendroglial tumours.[8]

9.2.2 Pathologic criteria

The pathological diagnosis of an oligodendroglial tumour remains subjective, and there is considerable inter-observer variability (see *Chapter 6 Diagnosis and pathology*). Diagnosis is most difficult for oligoastrocytomas for which consensus is difficult to achieve even amongst experienced neuropathologists.

9.2.3 Biologic markers

Refer to *Chapter 6 Diagnosis and pathology*

Role of 1p/19q deletions and other genetic abnormalities in management decisions

Combined 1p and 19q deletions (1p-/19q-) from tumour chromosomes have been identified as an important predictor of improved prognosis in patients with oligodendroglial tumours (see discussion below and in *Chapter 6 Diagnosis and pathology*) and should be performed in all tumours with

oligodendroglial features. 1p-/19q- predicts for a significant response to therapy, whether that will be radiotherapy or chemotherapy. The mechanism of this action is not understood.

Key point:

- 1p/19q testing should be performed on all tumours with oligodendroglial features.

Techniques used to assess: FISH versus LOH

Refer to *Chapter 6 Diagnosis and pathology* for further information.

9.3 Management

It is recognised that current optimal treatment modalities for OG and OA are unlikely to be curative and that there is a wide variation in the overall prognosis depending on the underlying pathology (grade II better than grade III, favourable cytogenetic aberrations), which may influence outcome irrespective of treatment types and the order in which they are administered.

9.3.1 Low-grade oligodendroglioma

In young patients who present with seizures, or who have an asymptomatic tumour found on incidental imaging, it may be possible to delay surgery for a period of time. However, care must be taken as it is well recognised that grade III tumours may present as non-enhancing tumours, particularly in patients older than 40.[9] Thus all patients should undergo a biopsy at presentation.

Surgery

Gross total resection of tumour has been associated with improved survival in most retrospective studies of low-grade gliomas[10,11,12], however the technical feasibility of gross total resection is limited by the proximity of tumour to eloquent brain and the extent of tumour infiltration. The classic definition of gross total resection in most studies is defined as the absence of residual enhancement on contrast-enhanced post-operative MRI scan and this in itself poses problems as up to 90% of grade II pure OG may not show initial enhancement.[2] In a recent study, inability to completely resect the tumour was related to diffuse tumour margin on T2-weighted MR images, oligodendroglioma or oligoastrocytoma histopathologic type, and large tumour volume.[11]

There are some consistent radiological findings with approximately 50% of OG demonstrating calcification, and over 80% of grade III OG and OA demonstrating post-contrast enhancement. Histological confirmation must still be obtained to accurately classify all tumours prior to treatment[13] and to permit molecular analysis.[14]

Recommendations	Level	References
All patients with suspected oligodendroglioma (OG) or oligoastrocytoma (OA) should undergo a biopsy for histological confirmation of tumour type and grade and to permit molecular analysis.	III	13,14
Maximal gross surgical resection is recommended where technically feasible, as this has been shown to increase survival.	IV	10,11
All suspected OGs or OAs must undergo histological confirmation as radiological features alone are inadequate for diagnosis and staging.	IV	9,13

Observation

Following surgery in pathologically confirmed low-grade tumours, observation (wait and see) is an acceptable approach in patients who do not have significant symptoms from the tumour, most commonly patients who present with seizures. This is based on the EORTC study comparing initial radiotherapy at diagnosis to delayed therapy at progression. The study showed that there was no difference in overall survival between the two groups, although not surprisingly progression-free survival was shorter in those in which treatment was delayed.[15] In most patients with oligodendroglial tumours there is a slow growth over time that averages an increase in tumour diameter of 4mm per year prior to anaplastic transformation that may not be readily obvious when comparing successive scans, but is more obvious when going back to an earlier scan.[16] Thus observation is an acceptable strategy for patients with gross technical resection and otherwise good prognostic factors of young age (<40 years), low tumour grade[17] and favourable cytogenetic aberrations (1p- / 19q-) which have been consistently associated with longer survival times,[14] thus allowing these patients to avoid the risk of long-term radiotherapy toxicities until disease progression.

Recommendation	Level	References
Observation only may be an acceptable strategy in grade II tumours with good prognostic features.	V	18

Radiotherapy

External beam radiotherapy has been used in the management of high- and low-grade gliomas in studies that have included both astrocytic and oligodendroglial tumours types. Unfortunately its efficacy has never been proven in a phase III study where accrual has been restricted to oligodendroglial tumours alone. There have been two prospective, randomised studies that have evaluated the effect of radiotherapy dose in low-grade glioma (LGG).

The NCCTG/RTOG/ECOG study randomised 203 adult patients with LGG, post-resection/biopsy, to 50.4Gy in 28 fractions over 5.5 weeks or 64.8Gy in 36 fractions over seven weeks.[19] On central review 70% of patients participating in this study had oligodendrogliomas or mixed tumours. At five years, there was no statistically significant difference in overall survival between the low-dose and high-dose treatment arms; 72% versus 64% respectively.

Similarly, a study conducted by the EORTC assigned 379 adult patients with pathologically confirmed LGG to either 45Gy in 25 fractions or 59.4Gy in 33 fractions. Not subjected to central pathology review, only 31% were reported as oligodendrogliomas or mixed tumours.

There was no significant difference in five-year progression-free (47% and 50%) or overall survival (58 versus 59%) between the low-dose and high-dose arms.[20] The optimal timing of radiotherapy in the treatment of LGG is controversial.

Recommendations	Level	References
External beam radiotherapy is a standard treatment for low-grade OG and OA.	II	19,20
The recommended radiotherapy dose for low-grade OG and OA is 50Gy in 2Gy fractions over six weeks.	II	19

An EORTC study (22845) performed a randomised phase III study comparing immediate post-operative radiotherapy to deferred radiotherapy upon progression in a population of adult patients with LGG. Both groups received 54Gy in fractions of 1.8Gy over six weeks. Pathology was centrally

reviewed in 81%. The majority of these patients had the diagnosis of a LGG confirmed but 26% were diagnosed with a high-grade tumour. The distribution of these patients between the treatment groups was balanced and a subgroup analysis which excluded these patients confirmed the findings of the intention-to-treat analysis.[21]

With a median follow-up of 7.8 years, immediate treatment was associated with an increase in progression-free survival (median 5.3 years versus 3.4 years) but not overall survival (7.4 years versus 7.2 years). Participation in the quality-of-life component of the study was optional and there were insufficient data to provide any meaningful analysis or conclusions. It is not possible therefore to ascertain whether the longer PFS observed in the treatment arm was countered by an increase in treatment-related side effect. Early seizure control, however, was better in the immediate treatment group.

An argument against early radiotherapy is the concern about delayed, treatment-induced neurocognitive dysfunction.[22] This is particularly pertinent in relation to the treatment of the asymptomatic or mildly symptomatic patient who may remain clinically stable for a protracted period without treatment. There is evidence that neurocognitive and neuroradiologic changes are associated with whole-brain radiotherapy and fraction sizes greater than 2Gy.[23–25]

To date, no large prospective randomised study has addressed this issue, however several case-control and comparative studies do not support the view that modern radiotherapeutic techniques using limited treatment fields and fractions sizes of ≤2Gy contribute significantly to long-term cognitive disability.[26] The largest of these studies[26] included 195 patients with LGG. This study suggested that the most deleterious effects on cognitive function were caused by the tumour itself and that other medical factors, especially the use of anti-epileptic drugs, are also implicated and deserve further study.

Recommendation	Level	References
Radiotherapy fraction size should not exceed 2Gy per day for high-dose treatments.	II	22–26

In general, immediate post-operative treatment with conventionally fractionated, limited field external-beam radiotherapy is recommended for patients with LGG presenting with mass effect, focal deficits or signs of raised intracranial pressure, particularly if resection of the tumour is limited.

A cumulative radiotherapy dose of 45–54Gy in fractions of 1.8–2.0Gy over five to six weeks with the treatment volume limited to the pre-operative tumour extent plus a margin of 1–2cm is currently accepted as standard.

It may be appropriate to defer radiotherapy until progression for the compliant, asymptomatic patient with LGG who has undergone a complete or near-complete resection without adverse clinical features. They should be monitored by repeated clinical and imaging review. Further discussion of the role of radiotherapy in LGG is given in *Chapter 7 Low-grade astrocytomas*.

Chemotherapy

In low-grade gliomas, it is not clear that chemotherapy adds any benefit. Chemotherapy and radiotherapy have not been directly compared for efficacy and safety.

Chemotherapy as primary adjuvant therapy post-surgery has been tested in a number of phase II studies, the largest of which was recently published.[17] One hundred and forty nine (149) patients with progressive low-grade gliomas were treated using standard temozolomide, correlating response to the presence or absence of 1p- /19q-. Fifty-three percent of patients achieved a response (partial response

= 15%; minor response = 38%), 37% had stable disease and 10% progressive disease. The median time to maximum tumour response was 12 months (range 3–30 months). The median progression-free survival (PFS) was 28 months. In 86 patients, tissue was available for tissue typing. In those with the classic 1p-/19q- deletions the response rate was significantly higher, and the response to chemotherapy was longer. Progression-free survival and overall survival were also significantly improved. A smaller study of 28 patients looked at response to combination procarbazine, lomustine and vincristine (PCV) chemotherapy prior to radiotherapy and showed a 52% response rate.[27]

Key point:

- Response to temozolomide chemotherapy correlates with 1p-/19q-.

9.3.2 High-grade oligodendroglioma

The issues and recommendations for surgery and radiotherapy for high-grade oligodendroglial tumours are the same as for other high-grade gliomas and are discussed in *Chapter 8 High-grade astrocytomas*.

Chemotherapy

High-grade oligodendroglial tumours are usually classified under the WHO system as grade III tumours. Some authors have referred to grade IV oligodendroglial tumours suggesting that they have a worse prognosis.

The chemosensitivity of oligodendrogliomas was first described in the high-grade group.[28] This led to use of chemotherapy in high-grade oligodendrogliomas and later in mixed gliomas. A larger prospective phase II study showed response rates of 75% of anaplastic 'pure' oligodendrogliomas.[29]

Kim reported 32 patients with mixed high-grade tumours[30] and seven high-grade oligodendrogliomas. They were treated with pre-radiation (19 patients) or post-radiation (12 patients) chemotherapy and 91% responded to the combined therapy. Median time to progression was 134 months (OA grade III), 12 months (OA grade IV) and 63.4 months (OG Grade III).[30]

Two randomised studies have been performed looking at the role of adjuvant PCV therapy and relating it to1p-/19q-. EORTC 26951 compared radiotherapy (RT) following surgery to RT followed by standard-dose PCV in 368 patients. They were required to have 25% or more oligodendroglial component on histology.[31] The median progression-free survival was significantly improved in those receiving chemotherapy initially (23 versus 13 months; p=0.0018) while overall survival was not significantly improved (40 versus 31 months; p=0.23). The five-year survival was 74% (RT and PCV), 75% (RT) for those patients with 1p-/19q- versus 33% (RT/PCV) and 28% (RT) with those without the 1p-/19q-. Clearly those with the 1p-/19q- have a different biology and better prognosis.

In the RTOG 9402 study, 289 patients were randomised to four cycles of intensive PCV before radiotherapy of 59Gy. 1p-/19q- was detected in 46% of assessable patients, and these patients also had a much longer survival regardless of randomised therapy. With the intensive PCV regime there was significant chemotherapy-related toxicity, however no cases of myelodysplasia or leukaemia were described. The five-year survival was 72% (PCV/RT) and 66% (RT) for tumours with 1p-/19q- versus 37% (PCV/RT) and 31% (RT) for those without the deletion.[1]

Recommendation	Level	References
Adjuvant PCV chemotherapy is not recommended for high-grade OG and OA as standard therapy because there is no improvement in overall survival.	II	1, 31

Oligodendroglial tumours with 1p-/19q- have a different biology to the other oligodendroglial tumours, and should be studied as a separate group. Sequential therapies, radiotherapy with subsequent PCV, initial PCV with subsequent radiotherapy with delayed chemotherapy are likely to be equally efficacious. As well, these studied have shown the limitations of the PCV, with side-effects related to progressive myelosupression and neuropathy due to vincristine.

A planned EORTC study will look at grade III gliomas stratified for 1p-/19q- using temozolomide in combination with RT in different arrangements to test whether the application of the Stupp protocol that is now standard in grade IV astrocytomas improves survival in oligodendroglial tumours without an increase in neurotoxicity.[32]

Carboplatin has also been shown to have activity in recurrent oligodendroglial tumours[33] although their dosing was fixed schedule rather than with Area Under the Curve Dosing (AUC) in patients with prior PCV therapy. Another study has shown favourable response rates with median time to progression of eight months.[34]

There is evidence that temozolomide can be effective in patients who recur following prior radiotherapy[35], and to a lesser extent in patients who have had prior PCV.

Twenty patients with recurrent aggressive oligodendroglioma post-radiotherapy who then responded to induction chemotherapy received myeloablative therapy with high-dose thiotepa and autologous stem cell grafts. The results were disappointing and associated with three toxic deaths with an encephalopathy related to the thiotepa.[36] More recently, the same treatment was used in newly diagnosed high-grade oligodendrogliomas.[37] The authors treated 39 patients (out of 69 in total) who completed three or four cycles of intensive PCV therapy, followed by high-dose myeloablative thiotepa with stem cell rescue. They showed that in this young population with a median age of 43, and good performance status, median progression-free survival was 78 months, and those who remained disease-free had an excellent level of function, although no formal neuropsychological testing was performed. The 1p/19q status was not formally assessed. It does suggest that such aggressive therapy is better tolerated in newly diagnosed radiotherapy-naive patients.

A recent survey of management of anaplastic oligodendrogliomas reported responses from 20% of members of the Society for Neuro-oncology. It suggested that there was a wide variation in the treatment of these tumours. 1p-/19q- was associated with a reduction in the number of patients receiving radiotherapy. Chemotherapy options included PCV and temozolomide most commonly, and concurrent chemoradiotherapy was the most commonly applied.[38]

Table 9.1 Chemotherapy regimens for high-grade oligodendroglioma

Drug/s	Dosing	Pros	Cons	Level of evidence	Refs
Temozolomide standard dosing	200 mg/m2 for 5 days every 28 days	Well tolerated and active No cumulative toxicity Can respond second time	Minimal	II	35
Temozolomide alternative scheduling	low-dose continuous one week on/one week off	May be useful in resistant tumours	Increased fatigue Increased lymphopaenia	IV	39
PCV	Procarbazine 60 mg/m2 Lomustine (CCNU) 110 mg/m2 Vincristine 2 mg/m2	Prior standard	Cumulative marrow toxicity limiting therapy Neuropathy & pain Monoamine oxidase inhibitor (MAOI) effects	II	29,30
Carboplatin	Area under the curve (AUC) 5–7	Good tolerability No cumulative toxicity Prolonged responses possible	Thrombocytopenia	III	33,34

9.4 Follow-up of oligodendroglial tumours

(See also *Chapter 14 Follow-up*)

There are no data identifying the ideal follow-up frequency for patients with oligodendroglial tumours. The principles are to closely monitor the patient initially to assess the tumour's pattern of behaviour, and then the interval of radiologic monitoring can be extended.

With high-grade oligodendroglial tumours imaging would be initially every three months and gradually prolonged. With low-grade gliomas, this interval can be lengthened and even extended after a period of observation to one-yearly intervals. Seizure management may also determine clinical frequency.

Imaging type for follow-up

MRI is the modality of choice given the higher degree of detail it makes available. For those in whom it is not possible (eg pacemaker or claustrophobia) CT scan is generally inferior.

9.5 Treatment of recurrence

While many of the principles relating to recurrent gliomas also apply to oligodendrogliomas, there are specific data to guide us.

In chemo-naive patients who have recurred following radiotherapy, there is evidence that both temozolomide and PCV are effective. Fifty-two patients who recurred following radiotherapy had a response rate to six cycles of PCV of 63% with a median time to progression for the whole group as ten months.[40] A more recent study of 38 patients treated with a planned twelve months of temozolomide at recurrence reported response in 20 patients. Median time to progression was 10

months for the group and 13 months for the responders. The drug was well-tolerated.[35] A larger study investigated 67 patients (39 patients had AP; 28 had AOA). The overall response rate was 46%. 1p-/19q- was detected in half of the patients and these patients had a significantly higher response rate, time to progression and overall survival.[41] In addition, there is also evidence in patients who have received prior chemotherapy that they can respond either to the same regimen in the case of temozolomide, or to an alternative regime such as PCV, temozolomide or carboplatin.[42–44]

As a significant proportion of these patients have relatively long survivals, re-irradiation becomes a possibility and should be discussed with a review of the prior radiotherapy regime including dose and treatment volume.[45] These options are discussed further in *Chapter 8 High-grade astrocytomas*.

The EORTC study reported five-year survival figures of 74% in patients with grade III oligodendroglial tumours with 1p-/19q- status, versus 34% in those without deletions in the group treated with radiotherapy and chemotherapy. The five-year PFS was 70% in the former, and 27% in the latter. Similar results were reported in the RTOG study.

Low-grade oligodendroglial tumours have median overall survival of nine years (1p+/19q+) and 13 years (1p-/19q-) respectively.[46]

Key point:

- Chemotherapy-naive patients with high-grade oligodendroglioma who have recurred following radiotherapy will often respond to chemotherapy.
- For recurrent high-grade OG, there may be a role for further chemotherapy and consideration of re-irradiation in patients with good performance status.

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10 COMPLEMENTARY, ALTERNATIVE AND UNPROVEN THERAPY

10.1 Introduction

Despite the significant improvement in conventional medical treatments, the outlook for many people with malignant glioma remains poor. It is not, therefore, surprising that an increasing number of patients and their carers will seek other therapeutic options.[1,2] These treatments are often referred to as 'complementary and alternative medicines' or 'CAM'. In combination with conventional approaches they are sometimes known as 'integrative medicine'.

Integrative medicine has been defined as 'conventional medicine working together with nutrition, supplements, exercise, and mind–spirit care, incorporating the insights and practices of complementary medicine, traditional non-Western medicine, and alternative medicine, when appropriate, directly with conventional approaches'.[3]

'Complementary' implies synergy with mainstream medicine either to improve the therapeutic outcome or to affect quality of life by ameliorating side-effects of treatment.

'Alternative' medicine includes therapies that are promoted as a substitute for conventional cancer treatments.

There is no unifying definition of CAM but the types of intervention may include:

- systemically administered treatments (plant and animal extracts, dietary modifications, vitamins, hormonal treatments, pharmaceuticals not usually used in cancer treatment, immune modulating substances)
- acupuncture
- massage and touch therapies
- psychological therapy including counselling, group therapy, relaxation, hypnosis, meditation and spiritual healing
- homeopathy
- non-invasive medical devices or procedures (eg delivery of low-intensity alternating electrical fields to the brain)

The prevalence and popularity of CAM use in the general population has been well documented in recent years, with rates of use ranging from 25% to 69% in Australia, UK, mainland Europe and USA.[4-6] At one comprehensive cancer centre in the USA over 80% of patients reported using CAM..[7] A study looking specifically at CAM use and quality of life in patients with primary brain tumours[8] found that 34% of patients reported using CAM and 74% of these stated that their physician was unaware. Higher performance status was the only factor significantly related to CAM usage. In the general cancer population other factors influencing increasing use include age (younger), sex (female) and pay status (higher).[7]

There are potential benefits as well as possible problems associated with the use of CAM in the treatment of brain tumours (as well as other malignant and non-malignant medical conditions).

10.2 Potential benefits

A major motivation of the interest in CAM is the perceived or real failure of mainstream medicine to provide desired outcomes. CAM offers the hope of access to more effective treatment with the implied promise of extended survival and improved symptom control.

Other potential benefits include:

- *Improved sense of psychological control*: initiating a strategy that is independent of the medical model gives the promise of exerting greater control over the disease process and the treatment itself.
- *Improved side-effect profile*: complementary strategies may ameliorate symptoms associated with conventional treatments such as chemotherapy and radiotherapy.
- *Access to less toxic treatment*: CAM is regarded as 'natural' and thus is assumed to have less toxicity.
- *The placebo effect*: 'placebo' is Latin for 'I will please' and refers to any medical treatment that is inert, that is, has no action. Numerous clinical trials have reported clinical benefits in subjects on the placebo treatment. Some CAM treatments such as homeopathy, faith healing and meditation may provide benefit through the placebo effect.
- *Restoration of hope* in the face of an often dismal prognosis.

In one recent study[7] that examined CAM usage in cancer patients, the most common reason reported for CAM use was a desire to feel hopeful (73%). Other reasons cited were belief that these treatments were less toxic and the desire to have more control over the decisions about medical care.

10.3 Possible problems

There are a number of real potential problems:

- The toxicity of many 'natural' remedies is either unknown or not readily available. There have been numerous reports of unexpected side-effects associated with CAM use in various cancers, for example, doses of selenium >1000mcg/day may cause muscle weakness, fatigue, peripheral neuropathy, dermatitis and liver damage.
- Potential interactions with conventional drugs are often not recognised or reported. One study estimated that of patients taking chemotherapeutic drugs and CAM, at least 27% were at risk of developing CAM–chemotherapy drug interactions.[9] The herbal product St John's Wort (SJW) is popular because of proposed anti-depressant activity. However, through the mechanism of hepatic enzyme induction, SJW has been shown to decrease the plasma levels of both irinotecan and imatinib (chemotherapy agents) in a clinically significant manner.[10]
- Purity of herbal remedies and dietary supplements can be problematic since in general the manufacturing quality and labelling are not as strictly controlled as pharmaceutical drugs. Contaminants and/or unrecognised ingredients have the potential to cause drug interactions and direct toxicity.[11]
- Many of the marketed CAM are expensive, adding an additional burden to an already stressful environment. Twenty percent of patients in one study admitted to spending more than US$100 per month on CAM.[8]

- The issue of 'false hope' may be important. Approximately one third of patients in one survey[7] expected CAM therapies to cure their disease. There is no real evidence outside of anecdotal reports that cure is a realistic goal.

10.4 Discussion

There are a number of interventions that may fall within the CAM definition that have shown promise, have demonstrated benefit or are part of mainstream management of cancer patients.

The definition of clinical benefit includes psychological and physical symptom control (quality of life [QOL]) as well as direct anti-tumour effects. It is important to distinguish between QOL effect and tumour control.

Generally 'alternative' treatments have been disappointing in terms of anti-tumour activity whereas 'complementary' treatments have good evidence to support activity in symptom control and QOL improvement.

The following are interventions with principally QOL benefit:

10.4.1 Counselling, support and psychological treatments

A range of psychological interventions are commonly used in cancer care (including brain tumours) and are part of mainstream management. There is high-level evidence from meta-analyses supporting this approach to improve well-being, although it does not affect survival.[12–14] However, lack of access to appropriately trained neuropsychologists and counsellors is a significant problem reported by brain tumour patients and their families.

10.4.2 Meditation and relaxation

The aims of meditation are to achieve relaxation and/or more spiritual goals. There are also specific relaxation techniques that do not involve meditation. There is clinical trial evidence that some form of relaxation reduces stress and pain and improves QOL of cancer patients.[15,16]

10.4.3 Acupuncture

Acupuncture is a method developed by traditional Chinese medicine using stimulation of acupuncture points on the body by needle, pressure, electric current or laser. There have been numerous clinical trials with conflicting results but there is evidence that acupuncture is useful in the treatment of nausea and vomiting (including chemotherapy induced) as well as pain.[17] This has been confirmed by a recent Cochrane review which identified acupressure as reducing the likelihood of nausea the day after chemotherapy (but not on subsequent days) and electro-acupuncture as reducing first-day vomiting.[18]

10.4.4 Massage and touch therapies

There is some evidence that massage therapy is helpful in the management of cancer pain. A recent randomised trial examining the benefit of aromatherapy massage in the management of anxiety and depression in patients with cancer reported no improvement in symptoms at ten weeks but a significant benefit at six weeks.[19] However, another randomised study of radiotherapy patients found that anxiety scores were significantly *worse* in aromatherapy patients.[20]

10.5 Systematically administered therapies

Some of the herbal and related compounds have been shown to reduce cancer- or treatment-related symptoms, for example, ginger and cannabis for nausea and vomiting, valerian for insomnia.[21]

Referring specifically to anti-tumour activity of CAM, the following points can be made:

- A systematic review of clinical trials of unconventional anti-cancer agents concluded that these treatments had not been the subject of appropriate early-phase trial development.[22] This fact together with the assertion that many CAM (such as homeopathy) are not suited to analysis by conventional clinical trial design means that there is a paucity of evidence to support their antineoplastic activity.
- In relation to malignant glioma, there is no high-level evidence that any complementary, alternative or unproven medicines have any significant antineoplastic activity

10.5.1 Homeopathy

This is based on the similarity theory, where the patient's symptoms are matched to side-effects of a known substance with the idea that 'like cures like'. The substance is diluted to a very low concentration (even to a level where only a single molecule may be present) prior to administration and attention is also given to aspects of lifestyle. Proponents of this treatment contend that by its nature it is not suitable for evaluation by traditional scientific instruments.

However a meta-analysis of all randomised placebo-controlled trials concluded that the clinical benefits were not entirely placebo effect.[23] There was no evidence of benefit for stroke or headache. Other neurological or oncological conditions were not examined.

The dilute nature of the treatment probably means that the risk of toxicity is very low.

Key points:

- There is no unifying definition of CAM and treatment that may fall within the definition of 'complementary', such as counselling, has high-level evidence to support its use.
- There is evidence for an increasing interest in and use of CAM.
- Antineoplastic activity of CAM in malignant glioma is supported by low-level evidence, such as case reports, and cannot be recommended.
- There needs to be a distinction between quality-of-life benefits and antineoplastic activity when assessing potential benefit.
- Quality of life and /or symptom management such as control of nausea and vomiting with acupuncture are supported by good evidence.
- Some of the modalities that may fall within the definition of CAM (eg counselling) are part of mainstream clinical practice and supported by high-level evidence.
- There are potentially very important toxicities associated with CAM caused by interactions with conventional medicines and primary toxicity.
- Many patients do not discuss CAM usage with their medical practitioner.
- For malignant glioma there is no high-level evidence for antineoplastic activity of CAM.
- Clinicians should inquire about the use of CAM in a non-confronting and non-judgemental way.
- Health professionals should not participate in the administration of unproven treatments.

10.5 Summary

There is little doubt that CAM will remain an integral and often unrecognised part of treatment strategies employed by patients with malignant glioma. In view of the potential toxicity and the frequent non-disclosure associated with CAM it is most important that treating physicians make direct and non-judgemental enquiry of their patients about CAM usage.

It is important that patients are thus able to obtain the best advice about the possible problems of toxicity and cost of CAM versus the potential benefits in terms of quality of life, symptom control and putative antineoplastic activity.

It is preferable to discuss all of these treatments in an atmosphere of collaboration rather than risk covert use of damaging substances or devices.

Comprehensive information about the safety and efficacy of CAM as well as clinical trials is available from several reputable web sites including:

- The Cancer Council Australia (<www.cancercouncil.org.au>)
- The M. D. Anderson Cancer Centre (<www.mdanderson.org/departments/CIMER/>)
- Memorial Sloan-Kettering Cancer Centre (<www.mskcc.org>)
- National Institute of Health (<nccam.nih.gov/>)

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11 SYMPTOM MANAGEMENT AND COMPLICATIONS

Patients with gliomas may suffer from a number of medical problems as a result of the primary disease or its treatments. Patients are frequently on multiple medications and clinicians should be aware of the risks of drug to drug and drug to complementary medicine interactions. Some of the treatment-related complications are dealt with in the chapters covering those treatments. Other common medical issues–seizure control, the use and complications of corticosteroids, skin reactions and thromboembolic events–are covered in this chapter.

11.1 Seizures

11.1.1 Seizure incidence and management

Most patients with tumour-related epilepsy have seizure as their presenting symptom. The incidence of seizures prior to diagnosis is 10–40%.[1,2] The incidence varies depending on the age of patient, and histology and site of tumour[3] with younger age and lower-grade tumours tending to be more likely to present with seizures.[4]

Seizures may be the only or principal source of disability. Seizures may arise as a result of the tumour or as a consequence of surgery. When disabling epilepsy occurs as a result of a low-grade glioma, ablative surgery is sometimes performed purely to eliminate seizures rather than for tumour control.[5]

Seizure types

Most seizures due to brain tumours are focal (partial) seizures. If the patient remains conscious during the seizure, it is known as a simple partial seizure, while complex partial seizures are those where consciousness is impaired (the patient does not respond or does not remember the content of the seizure).[6] Focal seizures may produce almost any episodic neurological symptom, from déjà vu or olfactory hallucinations through to focal twitching or paraesthesia. A focal seizure may evolve to a secondary generalised tonic-clonic seizure.

Prophylactic anti-epileptic drug therapy

Anti-epileptic drug (AED) therapies have been prescribed prophylactically to prevent seizures in any patient with a glioma or in those undergoing neurosurgery. However the evidence does not support such a strategy. A Mayo Clinic meta-analysis found only five relevant studies.[7] These studies often included all patients undergoing craniotomy (including non-tumour patients and extra-axial tumours), or all types and sites of intracranial tumour.[8,9] Studies of patients with glial tumours have included all grades of tumour. Both these issues make the results more difficult to interpret but there was no evidence of a benefit for prophylactic AED.

A small proportion of patients (perhaps 10%) develops seizures at the time of or within the first week after surgery.[2,10] The use of prophylactic anticonvulsants in this setting has been a controversial issue for many years. In the 1990s, a US survey found over 80% of neurosurgeons used prophylactic pre-operative anticonvulsants in patients with tumours of all types.[1] Few studies have looked specifically at the benefit of peri-operative anticonvulsants.[8,9] These have shown no clear benefit in reducing the likelihood of post-operative seizures.

Epilepsy develops later in the course of treatment in another small (approximately 10–15%) proportion of patients.[3]

In summary, there is currently no evidence to support the use of prophylactic anticonvulsants in patients with gliomas, either at presentation or at time of surgery.[1,7] If a patient has already been started on AEDs and remains seizure free, AED should be gradually withdrawn over a period of weeks.

Recommendation	Level	References
Prophylactic anticonvulsants are not recommended. However, once started, an anticonvulsant is best withdrawn over several weeks.	I	1,6

11.1.2 Epilepsy management

The main steps in epilepsy management are:

Confirm diagnosis

Not all episodic neurological symptoms in patients with gliomas are seizures. The diagnosis of seizures relies heavily on the history, including that provided by a witness to the event. EEG may provide confirmation but gliomas can cause EEG abnormalities without seizures. False negative EEG may also occur. If the nature of recurrent neurological episodes remains unclear, recording an episode with video-EEG monitoring may provide the diagnosis.

Counsel

Patients and their carers should be advised about the following issues including:

First aid

Minimising risks from seizures at home (bathing, heaters), at work (heights, machinery, vehicles) and at leisure (swimming, climbing).

When to call an ambulance

After the first seizure, for prolonged seizures (more than five minutes), second seizure before recovery from first seizure, repeated seizures within 24 hours, failure to return to consciousness after ten minutes, and if there has been a physical injury.

Driving

National standards for assessing fitness to drive have been published by Austroads[11] and include standards for patients with epilepsy (as well as those with brain tumours or a recent craniotomy). In summary, patients may not drive after their first seizure unless they remain free of seizures over the ensuing six months. After a diagnosis of epilepsy (recurrent seizures) is made and therapy started, driving may resume if no seizures have occurred in the next six months. Continuing seizures are not compatible with safe driving. More information on driving is given in *Chapter 13 Rehabilitation*.

Avoidance of seizure precipitants

Sleep deprivation, excessive alcohol, certain non-prescription and illicit drugs.

Medication issues

Avoidance of sudden withdrawal of AED, missed doses, timing, drug interactions

Prognosis

Only 60–70% of patients with focal seizures are fully controlled by AED therapy.[12,13] It should be explained to the patient that if the initial dose of the initial drug does not control seizures, there are many therapeutic options available to try to fully suppress seizures.

Support groups can be very helpful in providing information, practical advice and psychosocial support.

Decide whether to treat

A single seizure

The risk of further seizures in unselected patients is about 50%.[14] However this risk is increased in the presence of structural brain lesions, including gliomas and in patients with epileptiform abnormalities on EEG. Treatment after the first seizure has been shown to reduce the risk of subsequent seizures during therapy.[15,16] However, this benefit has to be weighed against potential side effects and the inconvenience of daily therapy. Compliance can also be a problem in situations where the need for therapy is less obvious to the patient. The decision to treat after the first seizure or to defer it to the next seizure may need to be individualised after discussing the advantages and risks with the patient.

Recommendation	Level	References
Anticonvulsant treatment should be commenced after the first seizure in patients with gliomas.	II	14,15

Recurrent seizures

In this situation, it is clear that an AED should be prescribed because the risk of subsequent seizures is very high.[17,18]

Choice of drug

Carbamazepine (CBZ), phenytoin (PHT) and valproic acid (VPA) are the standard agents in focal epilepsy (whether seizures evolve to generalised tonic/clonic [GTC] seizures or remain focal). CBZ and PHT are considered slightly more efficacious than VPA but the difference is small.[19] PHT and CBZ are both hepatic cytochrome p450 enzyme inducers, which may lead to accelerated metabolism of other hepatically metabolised drugs including corticosteroids and anticoagulants. PHT has the advantage of being available in an intravenous (IV) form but dosing must be individualised and its first order pharmacokinetics means that small changes in dose can produce large changes in serum level. IV PHT requires a loading dose of approximately 15mg/kg. The adequacy of the loading dose should be checked with a serum level performed one hour later. However, this will not predict the maintenance dose requirement. When immediate suppression of seizures is not required, an oral loading dose can be given. PHT serum levels are well correlated with toxicity and efficacy.[20.] A common error is to increase or decrease the dose in 100mg steps, which often results in an excessive change in level, resulting in seizures or toxicity. It is preferable in most circumstances to change the dose by one 50mg tablet or one to two 30mg capsules.

VPA may interfere with platelet function and number and many neurosurgeons prefer that it be avoided in patients undergoing craniotomy. VPA is available in an IV form.

CBZ should be introduced over several weeks with a slow increase up to an effective dose to reduce sedation, especially in the elderly. The newer AEDs–lamotrigine (LTG), topiramate (TPM), gabapentin (GBP), tiagabine (TGB), oxcarbazepine (OXC), leviteracitam (LEV) and pregabalin (PRG)–have some advantages, including a lower potential for drug interactions in most but are available in Australia under the PBS (with the exception of PRG) only where the standard AEDs are ineffective. They have not been demonstrated to have superior efficacy to CBZ. However, they can be very useful when seizures are not fully suppressed by standard AEDs. They should be added to the standard drug and then, if seizures become fully controlled, the standard drug may be tapered to establish whether the improvement is due to the combination or the additional drug alone.

Table 11.1 Characteristics of commonly used anti-epileptic drugs

	CBZ	PHT	VPA
Efficacy against focal seizures	++	++	+
Enzyme inducer	yes	yes	no
Unfavourable pharmacokinetics	no	yes	no
Usefulness of serum levels	somewhat	very	little
IV formulation	no	yes	yes
Effect on haemostasis	no	no	yes
Can be started at full dose	no	yes	no
Allergic skin reactions	yes	yes	no

AED interactions

CBZ and PHT are hepatic cytochrome P450 enzyme inducers and enhance the metabolism of many drugs, including commonly-used agents such as corticosteroids, warfarin and oral contraceptives[21], the dose of which may need to be increased to obtain the desired effect. CBZ metabolism is inhibited by erythromycin, clarithromycin, diltiazem and metronidazole[22], which can result in CBZ toxicity.

The ability of some AEDs to stimulate the cytochrome P450 enzyme system markedly accelerates the metabolism of many chemotherapeutic agents, including nitrosoureas, paclitaxel, 9-aminocamptothecin, thiotepa, topotecan and irinotecan, as well as the newer targeted molecular agents such as imatinib, gefitinib, temsirolimus, erlotinib and tipifarnib. This potentially reduces the effectiveness of these agents because the biologically active dose of these chemotherapeutic agents in brain tumour patients taking an enzyme-inducing AED (EIAED) may be much lower than in patients not taking EIAED.

Valproic acid has particular properties that complicate its use with specific chemotherapeutic agents. It inhibits the glucuronidation of SN-38, the active metabolite of irinotecan, and thus triples the AUC of SN-38 in laboratory animals. Additionally, it has been shown to inhibit histone deacetylase, a target of several chemotherapeutic agents in development including suberoylanilide hydroxamic acid (SAHA, Vorinostat) and depsipeptide (FK228). Its use in patients receiving these agents should therefore be avoided.[2]

Many chemotherapeutic agents induce coenzymes of the cytochrome P450 pathway and change the plasma concentration of concomitantly prescribed antiepileptic drugs. Cisplatin, vincristine, and doxorubicin can reduce the activity of carbamazepine and phenytoin. Methotrexate can reduce the plasma concentration of valproic acid. Doxorubicin and cisplatin can decrease the plasma concentration of carbamazepine or valproic acid. The toxic effects of valproic acid are increased when combined with cisplatin or nitrosureas. Combination of phenytoin with fluoropyrimidines (ie fluorouracil, tegafur, and capecitabine) increases phenytoin's toxic effects, and treatment failure has been noted in combination with tegafur. New anti-epileptic drugs such as gabapentin, levetiracetam, and pregabalin do not interact with other agents as they do not influence the cytochrome P450 or other metabolic pathways. To date, no or few side effects have been reported with levetiracetam in several series of patients with brain tumours who received concomitant antineoplastic agents.[23]

11.1.3 Monitoring treatment

Serum AED levels are most useful for PHT because of its first order pharmacokinetics.[20] However, evidence for the usefulness of levels for CBZ, VPA and the newer AEDs is lacking and clinical

monitoring is preferable to pre-emptive changes in patients without symptoms or signs of toxicity or continuing seizures.[24]

Cessation of AED therapy

When patients taking AEDs have had no seizures for a considerable time, there are two possible explanations: either the epilepsy is in remission and AEDs are no longer needed or the epilepsy is still active but suppressed by AEDs. Unfortunately, the only reliable way to discover which applies is to withdraw therapy and observe whether seizures occur. When this strategy was applied to a group of patients with epilepsy from various causes who had experienced two years without seizures, approximately 50% of patients remained seizure free.[25] Recurrence was more likely if there was any underlying neurological disorder.[25] The decision to withdraw or continue therapy in seizure-free patients must be individualised and should take into account the severity of the seizures, the presence of AED side effects, the need to continue driving (National standards require cessation of driving during medication taper and for three months thereafter[11]), the patient's views on continuing possibly unnecessary therapy and the acceptability of experiencing further seizures. In patients with high-grade tumours and a short life expectancy, the benefits of withdrawing therapy are usually outweighed by the high likelihood of seizure recurrence.

Recommendation	Level	References
If a decision to discontinue anticonvulsants is made, the drug should be withdrawn slowly, over two to three months.	I	1

Surgery for epilepsy

Surgical resection of gliomas producing seizures should be considered where AEDs are not controlling seizures, the epilepsy is significantly impairing quality of life and the tumour can be resected without unacceptable neurological deficit.[26] The low grade of a tumour and lack of neurological deficit should not argue against surgery and, in fact, may favour it because the benefits of surgery will extend over a longer lifespan than in higher-grade tumours. Extensive investigation is required to establish that the seizures are originating from the region of the tumour and to predict the effects of resection (both favourable and unfavourable). This includes video-EEG monitoring to capture both the clinical and EEG features of the seizures, MRI, functional MRI, ictal SPECT, inter-ictal PET and neuropsychological assessment.

11.2 Corticosteroids

The blood–brain barrier within a brain tumour and in the blood vessels surrounding the brain tumour is disrupted due to the loss of tight junctions between endothelial cells, increased pinocytosis in the endothelium and an increase in endothelial fenestrations.[2] Disruption of the blood–brain barrier results in accumulation of extracellular fluid in the brain parenchyma. Oedema contributes to the morbidity associated with a brain tumour.

The indication for treatment with corticosteroids is symptomatic cerebral oedema.[27] Treatment with corticosteroids has not been evaluated in a randomised clinical trial, but there is general agreement that patients with clinical and radiological evidence of oedema surrounding a brain tumour should be treated with corticosteroids. Patients undergoing radiotherapy to large volumes of brain benefit from corticosteroids, which reduce radiation-induced cerebral oedema and relieve headache and nausea.

No randomised trial has compared different corticosteroid agents in patients with brain tumours. Dexamethasone is generally used because it has less mineralocorticoid activity than the other corticosteroids.[2]

The optimum dose of dexamethasone is unknown. The usual starting dose is 16mg per day divided into two to four doses, but if necessary, the dose may be increased up to 100mg per day.[2] There has been no randomised trial comparing different doses of dexamethasone in patients with a malignant glioma, but lower doses (4mg or 8mg/day) may be equally effective. Doses as low as 2mg/d may be effective in preventing radiotherapy-induced cerebral oedema.

Recommendation	Level	References
Treatment with dexamethasone is recommended in patients who are symptomatic and have cerebral oedema. The usual starting dose is 16mg per day.	IIII	26

The risk of complications is related to the corticosteroid dose[28] and the duration of treatment. Therefore, the dose should be gradually reduced to the lowest amount that controls the patient's symptoms.[27,29] If possible, corticosteroids should be gradually withdrawn after radiotherapy has been completed.

Recommendation	Level	References
The dose of dexamethasone should be gradually tapered to the lowest amount that controls the patient's symptoms. Dexamethasone should not be discontinued abruptly.	IIII	26,28

Dexamethasone is usually not indicated in patients with asymptomatic oedema identified on imaging. Patients and their relatives should be provided with written guidance about the corticosteroid dose and potential side effects.

Patients should be monitored for side effects, especially hyperglycaemia, proximal myopathy and weight gain.

Recommendation	Level	References
Blood glucose concentrations, upper and lower limb power and weight should be assessed prior to starting corticosteroids and at regular intervals after treatment is started.	IIII	2

11.3 Gastrointestinal side effects

The risk of peptic ulcer disease and gastrointestinal haemorrhage is low when patients are treated with corticosteroids alone. The risk of peptic ulcer disease increases when corticosteroids are used with a non-steroidal anti-inflammatory drug (NSAID). Misoprostol, proton pump inhibitors and high-dose H2-receptor antagonists are effective in preventing chronic NSAID-related endoscopic gastric and duodenal ulcers, but only misoprostol 800 µg/day reduces the risk of ulcer complications such as perforation or haemorrhage.[30] Although misoprostol is the most effective agent in preventing peptic ulcer disease and its complications, its use is often limited by side effects such as diarrhoea. Proton pump inhibitors are usually preferred, because they are reasonably effective and they have fewer side effects. Treatment with a proton pump inhibitor should be considered in patients who have a high risk of peptic ulcer disease and gastrointestinal haemorrhage during treatment with corticosteroids: patients receiving high doses of dexamethasone; patients receiving a NSAID or anticoagulant with corticosteroid; and in patients with a past history of peptic ulcer disease.[2,27]

Recommendation	Level	References
Treatment with a proton pump inhibitor is recommended if a patient receiving corticosteroids is also being treated with a NSAID or an anticoagulant, or if the patient has a past history of peptic ulcer disease.	I	2,26
Treatment with a proton pump inhibitor should be considered in patients receiving dexamethasone in a dose exceeding 16mg per day, or 16mg per day for a long interval.	I	2,26

11.4 Bone effects

Patients receiving corticosteroids have an increased risk of bone loss and fracture. The risk of fracture is related to the dose and duration of corticosteroid treatment. Other risk factors include age, body weight, menopausal status and a previous history of fractures. Post-menopausal women have a threefold increase in the risk of a fracture within several months of starting corticosteroids, independent of the baseline bone density. Randomised trials for the prevention of steroid-induced osteoporosis have not been conducted in patients with brain tumours, but calcium supplementation with vitamin D[31], calcitonin[32] and bisphosphonates[31] have been effective in preventing bone loss in patients receiving corticosteroids for other indications. Bisphosphonates provide the best protection against corticosteroid-induced bone loss and fractures. Post-menopausal women with brain tumours who are started on corticosteroids usually should be treated with a bisphosphonate (alendronate 70mg per week, risedronate 35mg per week, or cyclical etidronate). Men and premenopausal women should have a bone density measurement to assess their baseline risk of developing osteoporosis. The use of osteoporosis prophylaxis should not be considered in patients with a very short prognosis.

Recommendation	Level	References
Prophylactic treatment for osteoporosis should be started in post-menopausal women receiving corticosteroids and in pre-menopausal women and men if the T score is less than -1.5. The Australian Pharmaceutical Benefits Scheme currently approves the use of risedronate in patients on steroids for greater than three months with a T score of less than -1.	I	30

Patients with brain tumours receiving corticosteroids may be at increased risk of *Pneumocystis jirovecii (carinii)* pneumonia. Prophylactic treatment may reduce the risk of *Pneumocystis jirovecii* pneumonia, but is not recommended as routine treatment except with concurrent temozolomide and radiotherapy.[1,2]

More information on corticosteroids is given in *Chapter 15 Palliative care*.

11.5 Skin reactions

11.5.1 Introduction

The skin of patients with gliomas can exhibit a wide and growing spectrum of cutaneous changes attributable to the tumour and/or the growing range and combinations of specific and supportive therapies used to manage this patient group. Cutaneous complications are highly visible, often discomforting, and serve as a constant reminder to patients that they have cancer and that their treatment is having toxic effects on the rest of their body and health.

The most common cutaneous changes observed in those with gliomas are those attributable to its treatment. Supportive care for cerebral oedema, seizures, mood disturbances and other tumour complications are also common causes of iatrogenic adverse reactions that involve the skin.

This section focuses on a number of common and important reactions detailing their presentation, differential diagnosis, associated toxicities, their significance and management.

11.5.2 Cutaneous drug reactions

Cutaneous changes in glioma patients can mimic other skin and multi-organ diseases. They can warn also of associated internal changes and toxicities. Traditional alkylating agents affect rapidly dividing cells making the skin, hair, nail matrix and mucosal toxicities common. Type A adverse reactions are attributable to a drug's known pharmacology and including its mechanism of action. These include myelosuppression, mucosal erosions and ulceration including mouth ulcers and erosions plus gastrointestinal upset, alopecia, and/or a petechial eruption which occurs as the platelet count falls to low levels due to myelosuppression that is typically limited to dependent areas and or occurring in areas of pressure or scratching.

Other cutaneous drug-associated reactions are classed as type B where their pathophysiology is not well understood. These are often described as unpredictable or 'hypersensitivity' such as the common exanthematic drug eruption (a spotty, non-confluent, red macular or slightly papular eruption that blanches with pressure and may or may not be pruritic). The diagnosis of a drug cause is supported by its time of onset, resolution on stopping the causative agents and its more rapid recurrence on rechallenge.

Both type A and B reactions can affect the skin, hair, nails and mucous membranes of patients. Although many adverse reactions to chemotherapeutic agents and anticonvulsants are solely limited to the skin, with many asymptomatic, mild and transient eruptions, others can be severe and life-threatening. Even a relatively mild cutaneous eruption can warn of severe internal organ toxicities. If a serious or severe drug reaction is suspected, the early cessation of all potentially causative drugs can reduce mortality.

Key point:

- When a new rash occurs in patients on anticonvulsants, liver and renal function should be checked to assess internal organ toxicity.

11.5.3 Cutaneous eruption of temozolomide and lymphocyte recovery

The frequency of rash reported in patients receiving temozolomide is close to that usually seen in placebo control groups for many neurology and oncology conditions such as patient groups being treated for epilepsy. The eruptions reported in association with this temozolomide have been poorly characterised–including analysis of their timing, response to withdrawal and/or rechallenge–nor were diagnostic skin biopsies taken. Thus their causality has not been well documented and assessed. It is thus recommended that you follow a guide similar to that outlined for glioma patients receiving anticonvulsant therapy.

The cutaneous eruption of lymphocyte recovery is more commonly seen in patients with leukaemia receiving chemotherapy, but can occur in other oncology settings. This is due to the return of tissue-infiltrating activated immunocompetent lymphocytes that usually occurs 6–12 days after a chemotherapy cycle and can be associated with a low-grade fever. The rash of lymphocyte recovery is usually slightly itchy, transient and exanthematous in nature.

11.5.4 Radiotherapy

Acute radiation skin reactions are common. This is because radiotherapy preferentially targets cells that divide rapidly, including those of the skin and bone marrow. This is reduced by increased fractionation, lower total doses and the use of multiple fields.

Acute cutaneous radiation effects can be minimised by the use of a soap-free emollient cleansers and the regular application of a non-fragranced, non-irritant moisturiser. Acute radiation effects are also known as radiation dermatitis or radiation skin reaction. They can begin within days to weeks with a transient faint skin erythema leading to a progressive although self-limiting skin erythema. Sorbolene is typically sufficient to relieve mild symptoms but on occasion a mild topical corticosteroid (eg 1% hydrocortisone) could be applied to affected skin to aid with symptoms of pruritis. Ulcers can occur but usually heal, but can recur if very high doses are given to the skin. If itchy, slightly eroded or weeping, colloidal oatmeal containing creams and cleansers are useful along with wet compresses using cool, slightly damp cotton towels or wraps for 30–60 minutes one to three times a day. If insufficient, mild to moderate topical corticosteroids should only be used sparingly and for brief courses in combination with an emollient used more generously.

Acute radiation dermatitis then usually resolves over weeks to months, usually resulting in a temporary increase in skin pigmentation. High doses usually result in loss of hair follicles, sebaceous along with eccrine glands. This reduces the skin's natural moisture and leads to dry more sensitive skin that has shed and lost its hairs. Doses over 45Gy are associated with permanent hair thinning or loss. Recovery may take months up to one year. If the skin does not show signs of atrophy and thinning, hair transplant can be attempted.

Over the following year the skin often becomes thinner, dryer and semi-translucent and the vessels more easily seen. It is critical to protect areas treated with radiotherapy from sunlight as they are subject to accelerated photo-aging and a greater risk of secondary malignancies.

Many kinds of rashes, irrespective of type and aetiology, can initially localise in areas of previous radiotherapy, whether this be recent (hours, days to weeks, or even months to years).

11.5.5 Clinical approach to managing a rash in a glioma patient on an anticonvulsant

Anticonvulsants carry the greatest risk of causing serious reaction in this patient group. Depending on the agent chosen, it is important not to exceed the recommended dosing schedule; and should a rash occur, the patient should contact their doctor. Current dosing guidelines have been designed to reduce the risk of serious reactions. Rashes are common in this group of patients and many non-drug-related eruptions can occur in patients on therapeutic agents. A rash during the first five days of therapy (in the first exposure) is usually due to a non-drug cause.

Patients who develop a rash in the first few months of anticonvulsant therapy, particularly phenytoin, carbamazepine, phenobarbitone and lamotrigine, need to be carefully evaluated. Rashes may only become apparent when dexamethasone dose is decreased or ceased. The most common anticonvulsant-associated eruption is an isolated, viral-like, eruptive rash usually described as morbilliform or maculopapular in appearance. This is self-limiting; however, a clinically similar eruption may accompany rare but more serious systemic hypersensitivity reactions.[51] Thus, all patients who develop rash during the first few months of anti-convulsant therapy should be instructed to immediately contact their physician for consultation.

Benign drug-associated eruptions typically peak within days and progressively settle over ten to 14 days. A benign, isolated, drug-related rash is spotty, non-confluent and non-tender. There should be only minor facial involvement and no periorbital puffiness; no facial or neck oedema; and no involvement of the mucosal surfaces of the eye, lip, or mouth. The diagnosis of a benign rash is

consistent with the absence of systemic symptoms such as fever, malaise, pharyngitis, anorexia or headache. There should be no lymphadenopathy, hepatomegaly or splenomegaly, and laboratory tests should be normal (ie complete blood count with differential, liver function tests, urea, creatinine, and urinary analysis). If a benign isolated rash occurs, the anticonvulsant dose should not be increased until the rash has entirely resolved; ideally, the dose should be reduced. Patients who develop a rash should be closely monitored and warned to contact medical staff should the rash worsen or new symptoms emerge. Pruritis associated with a benign rash can be treated with an antihistamine and/or topical corticosteroid. These drugs will not mask the development of a serious reaction. The characteristics of benign rashes are also relevant to the assessment of rash in the context of medications other than anticonvulsants including agents such as allopurinol.

Serious drug rashes are usually confluent and widespread or show prominent facial, neck, and upper trunk involvement. Serious rashes may be tender or have a purple 'purpuric' or hemorrhagic appearance that does not blanch with pressure. Serious drug rashes may involve mucosal surfaces. They are accompanied or preceded by symptoms and signs of systemic toxicity such as fever, malaise, pharyngitis, anorexia, or lymphadenopathy.[15] Rashes with any feature(s) suggestive of a serious reaction necessitate immediate drug cessation, and investigation and monitoring for internal organ involvement, particularly in the hepatic, renal, and haematological systems. Involvement of different organs can occasionally occur, and the severity of internal organ toxicities may increase despite drug cessation and may necessitate hospitalisation.[33] Serious reactions associated with lamotrigine should lead to prompt discontinuation of both the suspected causal agent and any other agent that might delay its elimination such as valproate.[34] It is important that another anticonvulsant from a different non-cross-reacting drug group be substituted as rapidly as possible, if immediate discontinuation is necessary, to reduce the risk of status epilepticus. There may be cross-reactivity in terms of clinical reactions to anticonvulsants (phenytoin, phenobarbital, carbamazepine, primidone and clonazepam). Sodium valproate may usually be substituted safely.[35] Early discontinuation of associated drug(s) after onset of a serious reaction improves patient outcome; however, drug discontinuation may not always prevent a more serious, life-threatening reaction from developing.[20]

11.5.6 Conclusions

A rash, particularly during the first eight weeks of anti-convulsant therapy, warrants evaluation by the treating physician and/or dermatologist. If a rash shows cutaneous features of a severe reaction or is associated with systemic symptoms, or involves mucosal surfaces, the anticonvulsant, as well as any concomitant unnecessary medications and any that could inhibit or delay its metabolism or elimination, should be promptly discontinued to reduce the consequences of a potentially life-threatening reaction. Thus the clinician needs to be aware of risks, clinical features and management of anticonvulsant-associated rashes. The decision to use an anticonvulsant in this group of patients should be based on a risk–benefit analysis, with the rare risk of serious rash weighed against the risks of seizures.

Recommendation	Level	References
Cutaneous drug eruptions with onset after ten days of exposure to an anti-convulsant, if associated with mucosal involvement or with systemic features, may be serious and require changing the antiepileptic medication to another group or category of drugs.	III	14

11.6 Venous thromboembolism

11.6.1 Introduction

Venous thromboembolism (VTE) (deep-vein thrombosis with or without its major complication, pulmonary embolism) commonly occurs in patients recovering from a variety of surgical procedures or in patients with incapacitating medical illnesses. Risk factors for VTE include genetic predisposition, immobility and malignancy. Thromboprophylaxis using medications that interfere with the normal coagulation process and with physical measures such as graded elastic stockings and intermittent pneumatic compression reduce the risk of VTE, but pharmacological measures carry with them an increased risk of haemorrhage, an issue that is a specific concern in the neurosurgical setting.

DVT usually starts in the calf, but by the time symptoms occur, 80% of patients have thrombus in popliteal or more proximal veins. In patients presenting with isolated calf DVT, the risk of proximal extension within a week has been variously assessed at 3–20%.[36] Thrombosis is often asymptomatic and resolved by the fibrinolytic system.

11.6.2 Incidence

In the general population, the annual incidence of DVT is about one per 1000, with a case fatality rate range of 1–5%.[37] The post-thrombotic syndrome, characterised by chronic pain, swelling and occasional ulceration of the skin of the leg, occurs in up to one-third of patients who have had a DVT.[38] The incidence of VTE complicating gliomas has been estimated at 20–30%, with reported peri-operative rates ranging widely between 2% and 60%.[2] The reported incidence is highly dependent on the sensitivity of the test used to detect VTE. The most sensitive test is a radio-labelled fibrinogen scan, which has been reported to detect asymptomatic DVTs in 72% of meningiomas and 20% of cerebral metastases.[39] Particularly high rates of DVT (11–75%) are also reported in patients after stroke, particularly when there is residual hemiplegia.[40]

A systematic review[41] revealed that in the first six weeks after surgery for glioma, incidence rates of VTE range from 3% to 60% depending on the prophylactic regimen used. Beyond six weeks post-operatively, the rates of DVT ranged from 0.013 to 0.023 per patient–month of follow-up. A 24% rate of incidence of symptomatic DVT was identified during 17 months of follow-up beyond the first six post-operative weeks. In six studies, the presence of leg paresis, histologic diagnosis of glioblastoma multiforme, age over 60 years, large tumour size, use of chemotherapy and duration of surgery over four hours were identified as risk factors.[41]

11.6.3 Pathogenesis of VTE in brain tumours

VTE is particularly common in brain tumours due to the release of procoagulant tissue factor[42] and fibrinolytic inhibitors (such as plasminogen activator inhibitor type I[43]) from tumour and surrounding cerebral tissues, producing low-grade disseminated intravascular coagulation. Higher plasma levels of D-dimer, lipoprotein A, homocysteine, vascular endothelial growth factor (VEGF), tissue plasminogen activator (TPA) and plasminogen activator inhibitor (PAI-1) have been identified in patients with gliomas.

11.6.4 Diagnosis of VTE

Deep venous thrombosis

The standard of care is the duplex Doppler ultrasound. The inability to compress the vein lumen is the principle diagnostic criterion in the interpretation of ultrasound examinations. This has replaced the other investigations, and is particularly sensitive in the detection of proximal deep venous thrombosis, with a lower negative predictive value for thrombosis below the knee. For proximal DVT, the sensitivity and specificity of compression ultrasonography is 95%, falling to 70–80% for calf DVT.[44] Recurrent DVT may be difficult to diagnose on ultrasound; up to 70% of patients have residual

abnormalities on compression ultrasound despite no evidence of recurrent disease in the year following a DVT.[45] Comparison of old and new studies may be helpful, and a negative D-dimer may be clinically helpful (*see below*).

Although scanning with radio-labelled fibrinogen is the gold standard investigation, it is not routinely available. X-ray venography is no longer used.

Duplex Doppler ultrasound is the investigation of choice for DVT

Pulmonary embolus

The diagnosis of pulmonary embolus (PE) is unsuspected until autopsy in approximately 80% of cases. PE is fatal in fewer than 10% of patients in whom it is diagnosed, whereas undiagnosed pulmonary emboli are fatal in approximately one third of patients. Patients who survive an acute PE are at high risk for recurrent PE and for the development of pulmonary hypertension and cor pulmonale.

Nuclear scintigraphic ventilation-perfusion (V/Q) scanning of the lung is indicated when the diagnosis of PE is suspected. A screening V/Q may be performed for patients with DVT even without symptoms of PE. A repeat V/Q scan may be appropriate before stopping anticoagulation in a patient with irreversible risk factors for DVT and PE, because recurrent symptoms are common and a reference 'post-treatment' V/Q scan can serve as a new baseline for comparison. In most clinical settings a 'high probability' V/Q scan may be considered diagnostic of PE; 87% of patients reported as having a 'high probability' V/Q scan will have a PE. Thirty percent of patients reported to have an 'intermediate probability' V/Q scan have a PE, while 14% of patients with 'low probability' V/Q scans will have a PE. Approximately 4% of patients with a 'normal' V/Q scan have a PE.

A CT pulmonary angiogram (spiral CT) has a low false negative rate, and detects large emboli in the first four generations of branches of the pulmonary arteries. CT angiography may not detect subsegmental embolism.[46] CT pulmonary angiography is an acceptable alternative to V/Q scanning, and may resolve indeterminate results.

Key point:

- Either a nuclear scintigraphic ventilation-perfusion (V/Q) or a CT pulmonary angiogram can be used to diagnose pulmonary embolus. A 'low-probability' V/Q scan does not absolutely exclude the possibility of a pulmonary embolus.

The place of the D-Dimer

The D-dimer test detects the production of fibrin degradation products consequent on the conversion of fibrinogen to fibrin. A negative D-dimer is a useful test of exclusion of VTE in combination with a careful clinical assessment, but a positive D-dimer has relatively low specificity.[48] False positive results are common in patients with infection and cancer and in post-operative patients and the elderly. Even increasing the cut-off level does not allow the D-dimer to be used reliably for the diagnosis of VTE. A negative D-dimer should be used with caution if the patient has had symptoms for more than two weeks, and if heparin has been administered prior to testing.

Recommendation	Level	References
The D-dimer, together with a careful clinical assessment, may be used to exclude a VTE and avoid unnecessary other investigations.	II	47

Prophylaxis of VTE

Non-pharmacological approaches: Mechanical thromboprophylaxis is particularly attractive in neurosurgery patients because of theoretical concerns about anticoagulant-related intracranial bleeding. Graded elastic stockings, intermittent pneumatic compression (IPC) and foot-pump devices carry no risk of bleeding. They require constant use, and compliance is difficult in the hospital and rehabilitation setting. They are, however, considered a safe and useful adjunct to pharmacological approaches. The mechanical approaches limit venous stasis and enhance systemic fibrinolysis. The failure rate with mechanical prophylaxis alone in surgery in glioma patients has been reported at between 3% and 9.5%.[49,50]

Pharmacological approaches: *Heparin* has been the mainstay of VTE prophylaxis. Aspirin is inferior and its use is not supported by available data. Unfractionated heparin (UFH) predominantly blocks activated thrombin (IIa). The main safety concerns are bleeding and heparin-induced thrombocytopenia (HIT), while UFH administration requires close monitoring of the activated partial thromboplastin time (APTT). UFH is administered intravenously as therapy for VTE or subcutaneously as prophylaxis. Heparin-induced thrombocytopenia and thrombosis (HIT or HITT) is characterised by a drop in the platelet count and thromboembolic events during heparin therapy–the risk of a serious thromboembolic event is approximately 30%, and a clinical suspicion of HITT is an indication for the immediate cessation of heparin and switch to another anticoagulant (danaparoid or lepirudin) and warfarinisation. A HITT screen should be performed after the cessation of heparin therapy, and urgent advice sought from a haematologist.

Low molecular weight heparins (LMWHs) are fractionated preparations of UFH restricted to the lower range of molecular weights. LMWHs offer comparable or superior efficacy to UFH. They do not require monitoring of the APTT and can be administered subcutaneously either once or twice daily, with excellent bioavailability. The risk of HITT is lower than for UFH. Disadvantages include a long half-life, irreversibility with protamine and reduced clearance in the presence of renal impairment. The half-life of intravenously administered UFH is 45–60 minutes, while the subcutaneous half-life of LMWH is about four hours, with some differences in the profiles of various LMWH preparations

Warfarin: The oral anticoagulant warfarin alters the hepatic synthesis of the vitamin K-dependent coagulation factors (factors II, VII, IX and X, and proteins C and S). The onset of action of warfarin is slow and widely variable, and dosing must be guided by close monitoring of the prothrombin time (standardised as the International Normalised Ratio or INR), and there are a large number of potentially serious interactions between warfarin and other drugs. The activity of warfarin is also modified by dietary intake. Warfarin is teratogenic in approximately 25% of cases in the first trimester of pregnancy.

Danaparoid (Organon) can also be used for thromboprophylaxis in patients with a history of HITTS or allergy to heparin preparations. *Lepirudin*, a hirudin derivative structurally unrelated to heparin, may also be used when heparin is contraindicated.

The place of thromboprophylaxis in the management of brain tumours

The benefit of thromboprophylaxis and associate risk of intracranial bleeding has been examined in small cohorts of patients. The pre-operative use of aspirin has been reported to reduce the incidence of VTE in a small cohort of patients with high-grade gliomas[51] but this has not been validated and is not generally recommended.

The risk of PE in neurosurgical patients has been reported to be as high as 5%, with a mortality rate of 9% to 50%.[52] The incidence of clinically overt DVT has been reported to range from 1.6 to 4%[53], but the incidence of objectively proven DVT has been estimated to range from 19 to 43% using ^{125}I-fibrinogen to screen for DVT and from 24 to 33% in clinical trials using venography to screen for DVT.[54]

The use of peri-operative and post-operative UFH or LMWH has been claimed to be safe in several uncontrolled series of neurosurgical patients. In four uncontrolled cohort studies, 507 patients were enrolled to receive anticoagulation. UFH 5000 Units was administered subcutaneously twice daily in 277 patients starting pre-operatively, and starting post-operatively in 138. The LMWH nadroparine was administered once daily post-operatively in 97 patients. There was a cumulative incidence of major haemorrhagic complications of 4% and a rate of reintervention of 0.4%.[55–58]

A double-blind randomised trial involving 307 patients undergoing neurosurgery, most of whom had brain tumours, confirmed that patients who received 40mg of enoxaparin daily together with thigh-length compressive stockings had a significantly lower rate of VTE (17%) than patients treated with compressive stockings alone (32%)[59]. The frequency of major bleeding episodes was identical in the two groups, while the incidence of minor wound haematomas was insignificantly increased in the enoxaparin arm. Similar findings were reported by Nurmohamed et al.[60] At a higher dose of enoxaparin (30mg every 12 hours starting in the recovery room) in patients with brain tumours was, however, associated with a high rate of intra-cerebral haemorrhage.[61]

A meta-analysis of prophylaxis with heparins in neurosurgery[62] evaluated four randomised controlled studies[59,60,63,64] that assessed the efficacy and safety of heparin prophylaxis in elective neurosurgery. Heparin prophylaxis resulted in a 45% relative-risk reduction of venous thromboembolic events (95% CI 0.35–0.66; p<0.002). Nineteen major bleeding episodes were recorded in 1022 patients. None was fatal, but heparin treatment resulted in a 71% relative-risk increase of major bleeding (95% Confidence intervals (CI) 0.69–5.4, p=0.24). Forty-five bleeding events were observed in 1022 patients for a median incidence of 4.4%, with the use of either UFH or LMWH resulting in a 100% relative-risk increase of bleeding events (OR 2.06, 95% CI 1.1–3.8, p= 0.02). Nineteen nonfatal events were recorded for a mean incidence of 1.8–2.3% in the heparin group and 1.4% in the non-heparin group. Of the 12 major bleeding events that occurred in treated patients, 11 were intracranial bleeding and one was gastrointestinal bleeding.

The number needed to treat was 7.7 for VTE and 16 for proximal deep venous thrombosis. The number needed to harm was 102 (105 for LMWH). The overall conclusion of the study was that LMWH and unfractionated heparin are effective for prophylaxis of VTE in elective neurosurgery without excessive bleeding risk. On the basis of this analysis, one major non-fatal bleeding event might be expected for every seven proximal DVTs or total 13 thrombotic events prevented.

A trial of prophylactic anticoagulation for six months[65] screened 563 glioma patients but only randomised 186 eligible patients to dalteparin or placebo. Twenty-one patients (11%) developed VTE within six months of surgery but there was no significant difference between the treatment arms. There were five (5%) major intracranial bleeds in the thromboprophylaxis arm compared with one (1%) in the placebo arm (p=0.2). Thus the role of prophylactic anticoagulation remains uncertain.

Nevertheless, there may be some patients judged to be at such high risk of bleeding that the benefit of thromboprophylaxis is likely to be outweighed by its risk, such as in intra-dural spinal cord surgery and some intracranial surgery.

Recommendation	Level	References
Peri-operative thromboprophylaxis with a LMWH is recommended for most patients with gliomas, although subcutaneous UFH is a reasonable alternative.	I	61
Prophylaxis is particularly appropriate for patients with high-grade gliomas and in elderly and immobile patients.	I	41
Thromboprophylaxis should be interrupted for surgery (no LMWH for at least 24 hours prior to surgery), resumed during the post-operative period, and continue until the patient is fully mobile. Mechanical measures to avoid VTE are recommended as adjunctive therapy.	III	48,49

Treatment of VTE

Less than 1% of episodes of VTE are fatal, but significant morbidity from post-phlebitic syndrome (symptomatic chronic venous insufficiency) develops in around 30% of individuals with lower-limb DVT. The rate of life-threatening bleeding in subjects taking warfarin is at least 0.25% per annum[64] and is higher once the INR exceeds 4.0, in the elderly and in patients with specific risk factors (including brain tumours).

Patients with brain tumours are perceived to be at increased risk of intracranial haemorrhage with anticoagulation because of the vascularity of tumours, and this has been used as a justification for the insertion of inferior vena caval filters instead of anticoagulation. However, Choucair et al[66] reviewed a total of 55 patients who, despite having residual tumour, received anticoagulation for at least three months, with no instances of intracranial haemorrhage. Ruff and Posner[67] retrospectively examined 103 unselected patients with malignant glioma anticoagulated with UFH (target 2.5 x control) followed by warfarin (INR target 2.5) for 6–14 weeks for DVT. Two of the patients (1.9%) developed intracranial haemorrhage, with one fatality, but over the same study period 2.2% of unanticoagulated patients developed spontaneous intracranial haemorrhage.

Traditionally LMWH has been used for initial anticoagulation to cover the period during which warfarin becomes effective, but there is evidence that LMWH may be more effective than warfarin in preventing recurrent VTE in patients with cancer.[68] In this study, comparing six months' therapy with dalteparin with warfarin, a hazard ratio of 0.48 for recurrent VTE was identified (p=0.002) in favour of dalteparin, with no significant differences in the rates of either major or minor bleeding. Although these data were not specifically derived from patients with brain tumours, continued anticoagulation with LMWH rather than switching to warfarin is considered a reasonable approach and avoids the difficulties of monitoring anticoagulation levels.

The appropriate duration of anticoagulation has not been studied in patients with brain tumours, and recommendations are extrapolated from other patient groups. Anticoagulation for three months is recommended for DVT occurring in the context of a precipitating event that has resolved (such as a completely resected benign tumour). Patients with pulmonary emboli are generally anticoagulated for six to twelve months. Prolongation of these intervals is appropriate in the setting of ongoing immobility or residual tumour, which is common in patients with high-grade glioma. The role of aspirin following the completion of anticoagulation for VTE is uncertain. VTE recurrence is generally regarded as an indication for indefinite anticoagulation. Smoking increases the risk of VTE and should be discouraged. Hormonal therapy (particularly high-dose oestrogen) is relatively contraindicated in patients who have had a VTE, although there are commonly competing factors in decision making.

The complication rate of IVC filters in patients with brain tumours was examined by Levin et al[69], who identified a 12% rate of recurrent PE and 57% rate of IVC or filter thrombosis with recurrent DVT or a post-phlebitic syndrome. The risk of PE is reduced by the use of concomitant anticoagulation with IVC filters, but with a remaining risk of recurrent DVT. In patients with brain metastases, Schiff et al[70] reported a 3% cerebral haemorrhage rate with anticoagulation (predominantly associated with over-anticoagulation) and a 40% rate of recurrent VTE requiring anticoagulation in patients with IVC filters.

At this stage, therefore, the data support a recommendation for therapeutic anticoagulation in patients with either gliomas or cerebral metastases with VTE rather than insertion of an IVC filter, except perhaps in the setting of metastases with a high risk of haemorrhage (melanoma, choriocarcinoma, thyroid and renal cancer). A CT scan to exclude intratumoural haemorrhage prior to anticoagulation is also prudent.

Fibrinolytic agents such as streptokinase and tissue plasminogen activator may be used to dissolve both venous and arterial thrombi and pulmonary emboli, but their use is contraindicated in the presence of recent surgery and intracranial lesions because of an unacceptable bleeding risk.

Vena caval filters are indicated to prevent PE in patients with VTE who have a contraindication to anticoagulation; recent neurosurgery may constitute such a contraindication. A removable IVC filter should be used in preference to a permanent filter, with a view to conventional anticoagulation after the post-operative period. Anticoagulation should be considered in patients with an IVC filter when a temporary contraindication to anticoagulant therapy is no longer present. Insufficient data exist to support a recommendation that all filter recipients should be treated with indefinite anticoagulation regardless of their risk of recurrent thrombosis. IVC filter insertion may be considered in selected patients with PE despite therapeutic anticoagulation. High intensity oral anticoagulant therapy or LMWH should be considered prior to IVC filter placement, particularly in patients with thrombophilic disorders or cancer.

Recommendation	Level	References
Anticoagulation with LMWH alone or followed by warfarinisation (for a period depending on the clinical scenario) is recommended as therapy for VTE in patients with gliomas. Exceptions may include anticoagulation in the immediate post-operative period, in which case a temporary IVC filter should be considered.	II	68

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12 PSYCHOSOCIAL CARE

12.1 Psychosocial impact of diagnosis

The diagnosis of any malignancy is distressing for the patient and their family. In the case of malignant brain tumours, distress may be compounded by fears about the cause of the cancer, and apprehension about loss of mental capacity: 'The brain is one's soul–to fear this loss is horrible'[1]. Psychosocial research specific to brain tumours is limited compared with other cancers such as breast and prostate cancer. If data specific to brain tumours are available this is stated in this chapter. Where there are gaps, research data from studies of mixed cancer populations are cited where appropriate.

12.2 Psychosocial issues specific to brain tumours

12.2.1 Personality change

Personality changes may have a profound impact on carers, even if the patient is not as aware of changes: 'Sometimes it was like caring for a total stranger with only glimpses of the man he used to be'[1]. Determining the precise aetiology of personality changes is difficult, with the relative contribution of tumour location potentially being modified by surgery, chemotherapy, radiotherapy and treatment with steroids. The concept of 'organic personality change' encompasses changes in habitual ways of thinking and acting following cerebral insult.[2]

Organic personality change may be manifest as increased mental rigidity, difficulty with motivation, changes in mood, or reduced empathy or capacity to respond to social cues. Specific focal syndromes have also been described, such as frontal lobe syndrome which is characterised by disinhibition, over-familiarity and poor judgment.[2]

Small studies have found that patients with left hemisphere lesions are more likely to experience difficulty with communication[3], while right hemisphere lesions are associated with lower scores on facial recognition.[4]

12.2.2 Physical changes

Seizures are a common problem for patients with brain tumours, and limitations on driving erode the independence of the patient, whose guilt about the added burden on family and carers may be considerable. If seizure control is poor there may be reluctance to leave the patient unsupervised and the patient may feel distress and grief at the necessity to be 'baby-sat' despite their adult status. *Chapter 11 Symptom management and complications* contains more detail on the management of seizures and the counselling of patients and their carers.

Physical deficits such as weakness, hemiplegia or sensory changes exert a direct influence on quality of life and limit the capacity of the patient to function autonomously, with obvious implications for psychological adjustment.

Despite the fact that they are not life-threatening, 'little problems' can act synergistically to cause considerable distress, yet these are often not explored by health-care professionals.[5] Changes such as residual facial weakness, weight gain related to treatment with steroids, or hair loss in a patient with stable disease may not be seen as serious by clinicians, but can be a source of anxiety and distress for the patient who perceives these changes to be highly socially visible.

12.2.3 Cognitive changes

It comes as no surprise that a tumour in the brain can cause disruption to brain function, and moreover that such disruption of brain function can give rise to changes in emotions, behaviour and cognition. The mechanisms by which brain tumours can compromise brain function include invasion or

displacement of brain tissue causing focal symptoms, disconnection of a given region of brain from a more distant region or disruption of widely distributed networks, production of generalised symptoms associated with raised intracranial pressure, seizures, abnormal hormones or disrupted endocrine function[6] and psychological distress. Added to these are the cognitive impairments associated with treatment.[7]

Brain tumour patients can present free of neurological symptoms, with subtle and variable cognitive impairment[8], or with disabling symptoms such as marked long-term memory deficits[9]. Patients with unequivocal cognitive impairment present with a wide range of heterogeneous cognitive impairments, however, strong associations between cognitive function and tumour location have been reported,[4] although tumour histology has been shown to be a poor predictor of cognitive impairment.[10] Others have also emphasised the importance of patient characteristics such as age[11] and premorbid intelligence and adaptive functioning[12]. One study of 701 patients with high-grade brain tumours reported that factors such as older age, poorer performance status and subclinical tumour progression may be more significant factors affecting cognitive function than radiotherapy or chemotherapy.[13]

The role of neuropsychological assessment is to characterise the nature and extent of cognitive dysfunction associated with a tumour, to provide a pre-therapy baseline against which future change can be measured, whether improvement resulting from treatments, therapies and rehabilitation, or decline associated with treatment side effects or tumour progression. Once the patient's cognitive strengths and weaknesses are known, this information can be used to develop recommendations and strategies for exploiting strengths to minimise the impact of weaknesses on daily functioning, and to assist in providing recommendations about capacity to return to a variety of roles including those of worker, driver, parent/caregiver, and even decision maker (testamentary capacity).

Recent studies have suggested that measures of cognitive function also have utility in predicting tumour recurrence when tumour-specific indices (with known structure–function association with the patient's tumour location) are examined.[14] Moreover, there is evidence that cognitive changes are evident before structural changes are seen on imaging.[15] In addition, one study found that measures of cognition, particularly verbal memory, were independently and strongly related to survival in patients with recurrent tumours.[16] In another patient series, cognitive function was found to be predictive of survival but only in the older patients.[17]

Although cognitive dysfunction is common in patients with brain tumours, many studies report relatively insensitive outcome measures–such as performance status or IQ scores–that fail to measure such disabling difficulties as impairment in executive function[18], so it is difficult to quantify the extent of the problem.

12.3 Assessment of cognition

It seems clear that if the goal is to detect the cognitive effects of these anatomically heterogeneous patterns of disease, a screening or brief assessment approach will not suffice and a more sophisticated and detailed assessment by a person with appropriate neuropsychology training is required[11,17,20] .

Recommendation	Level	References
Cognition dysfunction may not be apparent during brief consultations, and debilitating deficits will often only be detected by formal neuropsychological assessment undertaken by a trained health professional.	IV	14,15,17,19

Information gathered through interview and observation provides essential information to supplement the results of formal neuropsychological tests. Information should be obtained from both the patient and an independent source regarding noted and observed changes in cognition, mood and personality, with reference to day-to-day functioning and normal occupations, including the onset and course of each symptom. Discrepancies between patient self-report and informant observation are suggestive of limitations in patient insight, with implications for increased carer burden.

While individual practitioners use a variety of psychometric tests, the following parameters should be assessed:

- estimated pre-morbid intellectual abilities
- assessment of current intellectual abilities (including verbal and visuospatial abilities)
- attention regulation
- new learning and memory
- executive and adaptive skills (such as planning and organising thoughts and actions, complex reasoning and problem solving, initiation, impulse control, perseveration, sequencing, use of feedback/errors, social judgement, insight and self appraisal, speed/efficiency of information processing)
- mood and emotional functioning (including behaviour regulation during assessment)
- level of effort.

The process of forming a neuropsychological opinion involves interpretation of the psychological test results with due consideration of the following:

- the patient's pre-morbid ability (with reference to developmental, educational, and occupational attainments)
- level of application or effort
- psychosocial history
- cultural and linguistic background
- psychiatric and medical history
- mood and emotional functioning (especially, but not only, in terms of reaction and adjustment to diagnosis)
- pain and fatigue
- sensorimotor integrity
- current medications
- alcohol and/or drug use
- psychometric issues such as the quality of normative (preferably Australian) data and practice effects (if repeated assessment)

12.3.1 Subjective versus objective measures of cognitive dysfunction

While undeniably important in terms of understanding a patient's experience of their dysfunction, subjective complaints of cognitive impairment have been shown to be more strongly associated with emotional distress and fatigue than objectively measured cognitive impairment in cancer patients.[21] It has been suggested that brain tumour patients, especially those with frontal system tumours, may be especially at risk for under-reporting impairment due to impaired awareness and insight.[7]

Executive and adaptive dysfunction

Impairments of executive and adaptive functioning are common where brain tumours are located in the frontal lobes or in one of the numerous regions with rich connections to the frontal lobes.[22]

When tumours invade the frontal lobes or frontal system networks, patients can present with significant behavioural changes and subtle impairment of social or emotional functioning without obvious intellectual decline. Such patients may present well in brief interviews, perform entirely adequately on assessment of basic intellectual skills[12] and abilities, and perform very well on screening assessments such the Mini Mental State Evaluation (MMSE)[23]. In such patients, more sophisticated neuropsychological assessment of executive and adaptive functioning often reveals profound impairments in planning and organising, impulse control, initiating and carrying out goal-directed behaviour.[24] Such impairments, which can disrupt a diverse range of functions that are most identifiable as human, can have a devastating effect on the lives of patients and patients' support network alike.[25]

Recommendation	Level	References
Health professionals should consider the need for formal neuropsychological assessment to determine the nature of cognitive deficits and provide a basis for recommendations regarding capacity to return to previous roles, and to assist the patient and their family to adjust.	IV	17

Competence and decision-making

Given the often poor prognosis, making informed treatment choices and planning for future care is important. However, there is some evidence that patients and their families may not always be open in communication, and few couples openly discuss death and dying although in some instances there may be a mutual unexpressed understanding of the situation.[26]

Legally, an adult patient is able to make a decision regarding medical treatment if they have the ability to understand the nature and the consequences of their decision. It is up to the treating practitioner to determine whether a patient is competent to make a treatment decision. A patient may be legally competent to make some decisions but not others, depending on the extent of their cognitive impairment. The more serious the consequences of the decision, the greater degree of competence required. Thus a patient may be competent to consent to a minor form of treatment but not competent to make a decision to consent to the withdrawal of life support. If the treating practitioner is in any doubt about a patient's competence they should seek another opinion from another suitably qualified practitioner.

A competent adult patient has an absolute right to refuse medical treatment, including potentially life-saving treatment. A patient's refusal may be for whatever reason the patient chooses even if the decision may lead to the patient's death. It does not matter if the health professionals involved in the patient's treatment, family members or anyone else considers the refusal to be unreasonable, irrational, or not in the patient's best interests. The presumption of competence will not be overridden because the patient's decision to refuse medical treatment will lead to their death. To provide

treatment to a competent patient against his or her express wishes amounts to assault and leaves a health-care professional vulnerable to legal action.

Key point:

It is up to the treating practitioner to determine whether a patient is competent to make a treatment decision.

Recommendation	Level	References
A medical practitioner must provide the patient with information to allow the patient to make an informed decision about treatment. A patient must be advised about the nature of their condition, any alternative forms of treatment that may be available, the consequences of those forms of treatment, and the consequences of remaining untreated.	I	27

A competent adult patient may express an intention in an advance directive to refuse medical treatment in the future at a time when he or she may no longer be competent to make a treatment decision. At the time of making the advance directive the patient must be mentally competent and properly informed about the consequences of the directive, and the advance directive must apply to the clinical circumstances existing at the time the directive is sought to be relied upon. Advance directives have been given express statutory recognition in the ACT, Northern Territory, Queensland and Victoria. More information is given in *Chapter 15 Palliative care*.

If a medical practitioner believes a patient is cognitively impaired and is not capable of making a treatment decision and there is no valid advance directive, the medical practitioner has a legal responsibility to obtain consent for the proposed treatment from a surrogate decision-maker. The most significant exception to this is the provision of urgent medical treatment. Although the definition of 'urgent' varies from State to State, the common thread is that the medical practitioner must believe that the medical intervention is necessary to save the life of the person or to prevent serious damage to the person's health, or to relieve a patient's suffering from or continuing to suffer from significant pain or distress. In South Australia and the Northern Territory this decision must be based on the opinion of at least two medical practitioners, although in South Australia, one practitioner will suffice if it is impractical to have a second practitioner involved.

NSW, Victoria, Tasmania, Western Australia, South Australia and Queensland have legislation enacted to enable the 'person responsible' or the 'statutory health attorney' (Queensland) to give consent for medical or dental treatment. The 'person responsible' is defined in the relevant legislation and may include a spouse, a near relative, a close friend or primary carer of the patient. The legislation in each State also provides a hierarchy that must be followed before the next person in the hierarchy is authorised to give consent on behalf of the patient. The hierarchy and any other prescribed steps must be followed.

The process of obtaining consent from the person responsible (the surrogate decision-maker) still requires the practitioner to provide such information to that person to enable that person to make an informed decision. However, the legislation does not enable the person responsible to give consent for medical or dental treatment that is classified under the legislation as 'special' (NSW, TAS, WA, VIC, QLD) or 'prescribed' (SA, ACT) treatment. Special or prescribed treatment includes procedures such as sterilisation, termination of pregnancy or experimental procedures. All Australian States prohibit the performance of this type of surgery or procedure without the consent of the relevant statutory body. The Northern Territory (unlike other States) defines this category of procedures as 'major

medical' procedures. In several States it is an offence punishable by fine or imprisonment to provide this type of medical or dental treatment, other than in accordance with the relevant legislation. The Victorian legislation provides that any medical practitioner who carries out this category of treatment other than in accordance with the legislation may be guilty of professional misconduct.

The Australian Capital Territory and the Northern Territory do not have a provision to enable a near relative, spouse or carer to give consent on behalf of person with cognitive impairment. Therefore, the appropriate person to provide consent is the person legally appointed as guardian under the relevant Act. If no guardian has been appointed, and the treatment does not fall under the definition of 'urgent' medical treatment, the medical or dental practitioner should not provide treatment until the appropriate steps have been taken to have a guardian appointed as required by the legislation.

Several States have included in their guardianship legislation a provision to enable some treatment to be provided without consent of the patient or the 'person responsible' as long as the prescribed steps set out in the relevant Act are followed. For example in NSW, if the guardian or person responsible cannot be located, a medical practitioner may provide 'minor treatment'. This is defined under the NSW legislation as being treatment that will most successfully promote the patient's health and wellbeing and the patient does not object to the treatment being administered. The treating practitioner must certify these matters in the patient's record and state that the treatment is necessary. Minor treatment is considered to be treatment that will not cause any distress or is of a temporary nature and the benefit of the treatment will outweigh the side effects of the intervention. For example, in NSW this includes the giving of a general anaesthetic or other sedation to manage a fracture or dislocation or the administration of medications that affect the central nervous system for the purpose of providing an analgesic, anti-pyretic or antihistamine. The legislation in Tasmania, Queensland and Victoria also has provisions allowing for minor treatment to be carried out in certain circumstances.

The variations between each State are such that it is impossible to cover all of the issues here. Health-care professionals and medical practitioners in particular who regularly deal with patients with a cognitive impairment should be aware of the legislation that applies in their State or Territory. If there is any doubt about a particular case, legal advice should be obtained.

For decisions at the end of life for cognitively impaired patients, it is not clear in some States or Territories whether the relevant statutory body is legally empowered to make decisions to withhold or withdraw life-sustaining treatment, where there is no valid advance directive or surrogate decision-maker.

In these circumstances, a medical practitioner's obligation is to treat the patient in accordance with the patient's best interests. In forming a judgement as to what is in the best interests of the patient, factors to be taken into account by the medical practitioner include the personal circumstances of the patient, and information from family and/or carers about the choice the patient might have made in the circumstances. In decisions at the end of life it is reasonable to take account of the invasiveness of the treatment and the indignity to which a person has to be subjected if life is prolonged by artificial means.

A medical practitioner is not required to provide treatment that is futile or treatment that is not clinically indicated, nor is there any obligation to prolong the life of a dying patient by any means available regardless of the quality of the patient's life. There may be differing views about the futility of treatment. In the case of a dispute about a patient's treatment between a patient's family and health-care professionals, an application may be made to the court by either party to resolve the dispute. The Supreme Courts in each State and Territory have the power to act in the welfare of a person who is unable to care for themselves. The Court can make decisions for incapable persons in their best interest, including a decision to cease life-sustaining treatment.

The legal requirements for competent decision-making also apply to a patient's decisions about financial matters, both during their remaining life and after they die. The various State and Territory

statutory bodies are able to make decisions about a patient's financial matters where they are not competent to do so and the patient has no guardian or has not assigned power of attorney.

The ability to make a valid Will depends on a patient having the required testamentary capacity to do so. In general terms, to have testamentary capacity, the patient must:

- Understand the nature and the effect of the Will.
- Understand the extent of the property they are disposing by the Will.
- Comprehend and appreciate those who should be considered as their beneficiaries.
- Not have a disorder of the mind that 'shall poison his affections, pervert his sense of right, or his will in disposing of his property and bring about a disposal of it which, if his mind had been sound, would not have been made'. [28]

The relevant legislation in each State and Territory is:

NSW	Guardianship Act 1987
SA	Guardianship and Administration Act 1993 Consent to Medical Treatment and Palliative Care Act 1995
TAS	Guardianship and Administration Act 1995
WA	Guardianship and Administration Act 1990
QLD	Guardianship and Administration Act 2000 Powers of Attorney Act 1998
NT	Adult Guardianship Act Powers of Attorney Act Emergency Medical Operations Act, 1992 Natural Death Act 1988
VIC	Guardianship and Administration Act 1986 Medical Treatment Act 1988
ACT	Guardianship and Management of Property Act 1991 Medical Treatment (Health Directives) Act 2006

Recommendation	Level	References
Health professionals should determine the capacity of the patient to make decisions, and be aware of legislation that applies in the case of patients who are not competent to make decisions. Health professionals should be prepared to review this capacity as it may change over time.	I	27,29

12.3 Quality of life

A study of 50 patients with primary brain tumour found that quality of life was affected by a number of factors: the extent of tumour involvement (with bilateral involvement leading to worse quality of life than unilateral), poor performance status, being female, having been divorced, undergoing aggressive treatment, and being unable to work.[30] Motor deficits, confusion and dysphasia have also been found to reduce quality of life.[31]

Patients with tumours in the anterior right hemisphere have been reported to have higher quality of life.[32] Freedom from depression, having an active social life and level of energy, and fewer symptoms are also associated with higher quality of life.[33]

In addition to the direct impact of the tumour and surgical treatment, other treatments such as radiotherapy can affect quality of life. A prospective study reported that 42% of patients experienced considerable tiredness after radiotherapy.[34]

There are few data about the quality of life of patients who survive brain tumours for extended periods. In 57 patients with stable disease, quality of life was found to be related to depressed mood, anxiety and performance status.[35] One study of ten patients who had survived glioma for five years found that only one patient was working full-time, and impairments in attention, role functioning and capacity to participate in leisure activities were prominent in nearly all patients.[36]

Quality of life for patients with recurrent disease is determined by multiple factors, and is poorer than in those with stable disease. The existential issues confronting patients and their families are considerable, but often not expressed.[37] Cognitive deficits were universal in a study of 94 patients, and anxiety was higher in those more recently diagnosed with recurrence.[38] Interviews about quality of life with bereaved relatives reveals that cognitive and personality change exert a powerful influence on their appraisal of quality of life for patients with advanced disease.[39]

When faced with a poor prognosis, patients may use alternative therapies in the belief that conventional medicine is 'not very effective'. A study of 167 patients with primary brain tumour found that 24% used alternative therapies, and of these patients, two-thirds believed that the therapies were useful in terms of improving their energy, or physical or mental wellbeing. This study did not find any difference in quality of life between users of alternative therapies and non-users.[29] Use of alternative therapies is described in more detail in *Chapter 10 Alternative, complementary and unproven treatments*.

Key point:

- Cognitive and personality changes are common and have a powerful adverse impact on quality of life.

12.4 Psychological disorders

12.4.1 Anxiety and depression

Extent of the problem

Half of patients treated for primary brain tumour self-report depressed mood.[33] Twenty-eight percent of a sample of 89 ambulatory patients with brain tumours met Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria for depression. The Glioma Outcomes Project analysed data from 598 patients in the early post-operative period. There was a marked disparity between patient self-reports of depression and physician assessment of depression (93% versus 15%), and even when physicians considered that the patient was depressed, few patients were referred for specialist treatment.[22] Those patients who were identified as depressed by their physician had significantly

shorter survival than those not identified as depressed, and more post-operative complications. At six-month follow-up, patients being treated with corticosteroids were more likely to be depressed than not depressed.[22]

Risk factors for anxiety and depression

There is some evidence about factors that may predispose to the development of depression in patients with brain tumours. Females have been reported to have higher scores on measures of anxiety and depression than males[40,41], and those with left hemisphere lesions have higher depression scores than those with right hemisphere lesions. Frontal location of tumour has been found in one study to be a risk factor for depression, along with having a family history of depression.[42] Not surprisingly, high levels of physical disability and cognitive dysfunction are associated with high levels of psychological morbidity.[43]

The general cancer literature has identified a number of risk factors for the development of anxiety or depression, and it is worthwhile to document these factors with a view to referral for specialist psychosocial assessment and treatment, and early identification and intervention.

Table 12.1 General risk factors for increased psychosocial distress

Characteristics of the individual	Characteristics of the disease and treatment
Female	At the time of diagnosis or recurrence during advanced stage of disease
Younger (less than 55 years of age)	Poorer prognosis
Single, separated, divorced or widowed	More treatment side-effects
Living alone	Greater functional impairment and disease burden
Children younger than 21 years	Experiencing chronic pain
Economic adversity	Fatigue
Lack of social support, perceived poor social support	
Poor marital or family functioning	
History of psychiatric problems	
Cumulative stressful life events	
History of alcohol or other substance abuse	

Adapted from *Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer* 2003. Reproduced with permission.[44]

Recommendation	Level	References
Patients who have risk factors for increased psychological distress should be offered referral for psychosocial treatment as this minimises the likelihood that they will develop significant distress	I	45

Anxiety versus a disorder

Anxiety is a feeling of apprehension and worry. In the context of a brain tumour, anxiety is often related to the prognosis, treatments and symptoms. While some degree of anxiety is normal in response to the diagnosis, a disorder should be considered when the distress interferes with the capacity of the person to make treatment decisions or undergo treatment (such as having panic attacks when attending for radiotherapy treatments), or it interferes significantly with sleep and appetite, social and occupational functioning. Similarly, a diagnosis of depression should be considered when mood is severely and pervasively depressed, there is inability to enjoy normally pleasurable activities,

or there is an adverse impact on social and occupational functioning. Depression may also be associated with decreased energy, feelings of worthlessness or guilt or recurrent thoughts of death or suicide.[44]

Unfortunately patients may be reluctant to express symptoms of anxiety or depression because of concern that this makes them appear weak or ungrateful, so health professionals may need to ask specific questions to elicit symptoms. The following suggested prompts are adapted from *Clinical practice guidelines for the psychosocial care of adults with cancer.*[44]

- Can you tell me how the diagnosis has affected you emotionally?
- Are there any particular things that make you anxious? How would you say this is affecting your life?
- Would you say that you have felt really sad or depressed?

Treatment

The approach to treatment of anxiety and depression in patients with cancer generally involves a combination of pharmacotherapy and psychotherapeutic support.[46] Specific psychological therapies are listed in the Table 12.2 below, along with documentation of their effectiveness. Further information about treatment of distress is available in *Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer,* which can be downloaded from <www.nhmrc.gov.au/publications/synopses/cp90syn.htm>.

The pharmacological treatment of anxiety may include use of antidepressant medication, neuroleptics, and benzodiazepines. For acute anxiety, benzodiazepines are often helpful; with the shorter-acting agents such as lorazepam and oxazepam being safest although they may be associated with a risk of break-through anxiety.[47] Antidepressant medication is generally well-tolerated and effective in patients with cancer.[48]

While clinical experience suggests that antidepressant medication may be of benefit in patients with brain tumours[49], it is particularly important to be aware of the risk that antidepressant medication may lower seizure threshold in this population.

Key point:

Identification of depression and anxiety is important as these disorders can be effectively treated with a combination of supportive psychotherapy, cognitive and behavioural techniques, and pharmacotherapy

Delirium

Delirium is a syndrome of cognitive disturbance and affective arousal, common in patients with cancer, but often misdiagnosed and mistreated. Patients may experience disturbances in a variety of functions including level of consciousness, attention, thinking, perception, emotion, memory, psychomotor behaviour and sleep/wake cycle, the pattern of disturbance typically fluctuating over the course of a day.[47] Delirium occurs in between 15 and 20% of hospitalised cancer patients, although the figure appears to be much higher in those with advanced disease.[47]

Whilst the agitated, disruptive patient is likely to attract the attention of health professionals, hypoactive cases, which account for up to 50% of cases of delirium, may go undetected or be misdiagnosed as depression.[50] Agitated disruptive behaviour due to delirium may similarly be misdiagnosed as anxiety or personality disorder. The experience of delirium is highly distressing for

patients and their families, with over half of patients recalling their delirium experience, which is often characterised by disturbing psychotic symptoms.[51]

Key point:

- Delirium should be suspected in any patient who demonstrates an abrupt change in behaviour, personality or mood.

The treatment of delirium focuses on identification and treatment of the underlying causes, along with attention to fluid and electrolyte balance, nutrition, and measures to help reduce anxiety and disorientation, such as constant re-orientation, use of a night light, correction of hearing and visual impairment.[52] Pharmacological treatment of delirium has traditionally been with low-dose typical antipsychotic medications such as haloperidol which, while effective, carry the risk of extra-pyramidal side-effects.[47] There are few well-designed studies examining the use of the atypical antipsychotics in delirium, however risperidone and olanzepine appear to be safe and effective.[50]

Recommendation	Level	References
When delirium is suspected, the cause must be identified urgently and treatment of the cause must take place while pharmacological and non-pharmacological treatments are initiated to reduce the distress of the patient and their family.	IV	46

Organic mental disorders

Patients may experience mental disorders without the clouding of consciousness that is central to a diagnosis of delirium. In these instances, prominent symptoms include anxiety, mood disturbance and hallucinations, and sometimes delusions.[43] Organic mental disorders can be due to the direct effect of the brain tumour and local oedema, or indirect effects of disease or of treatments such as corticosteroids, or a combination of these factors. Management involves investigation and treatment of the cause as appropriate, as well as treatment of the psychotic symptoms with antipsychotic medication such as risperidone 0.5mg/day, titrating up to 4–6mg/day depending on clinical response and side-effects. On rare occasions, patients may require inpatient management in a psychiatric unit as an involuntary patient because they lack insight and the nature of their condition means that they pose a risk to themselves or others.

Recommendation	Level	References
If organic mental disorder is suspected, the patient must be assessed for treatable causes, and specialist psychiatric advice obtained about management.	IV	46

12.5 Issues facing families and carers

Levels of distress in the relatives of 75 patients with brain tumours have been reported as higher than the levels of distress amongst patients themselves. [34]

Family members can feel isolated from others who fail to appreciate the burden of care they are facing when the patient has personality or cognitive deficits[53], and this makes it harder to cope[54]. In one study of the adjustment of 95 caregivers of patients with malignant brain tumours, 88% reported that the patient experienced at least one neuropsychiatric symptom, the most common being dysphoria or depression. Levels of depression in caregivers were linked with the number of neuropsychiatric

symptoms experienced by patients.[55] Whilst assisting patients with activities of daily living does pose a burden on schedules and health, this does not affect the mood of caregivers in the way that neuropsychiatric symptoms do.[55] This is consistent with research demonstrating that even after bereavement, very few relatives considered that quality of life for the patient had been good or acceptable, irrespective of the time lived without severe physical disability, if the patient initially experienced marked psychological change or distress.[39] If the patient's quality of life is poor, carers may feel ambivalent about the patient's survival, but such feelings may be a source of guilt.[56]

There may be substantial differences between patient and caregiver perception of difficulties. One small study found that in one-third of cases, the patient and caregiver disagreed about the extent of residual problems.[57] Thus it may be difficult to maintain a balance between supporting and assisting the patient and 'taking over'.[5] Relatives may see their role as remaining strong in order to protect the patient. In some instances relatives may try to avoid explicit discussion about the prognosis because of the belief that this would be harmful for the patient.[34] Contrary to popular belief, in general, expression of thoughts and feelings helps patients and their families cope.[58]

The inevitable changes in roles and relationships cause tension and distress.[59,60] Relatives may struggle to adjust to the changed personality of the patient, but find that there is little external recognition of the grief this poses.[61] Lack of support exacerbates role strain for families and carer, who often have little respite from their caring role.[1]

Relatives describe difficulty in obtaining medical information and making informed treatment choices, and express the need for discussion about quality-of-life issues in making treatment decisions along the continuum of treatment, not only when no further treatment options exist: 'Quality of life is only raised when there is no quantity'[53].

(For further discussion of issues facing carers see *Chapter 2 Approach to the patient.*)

Key point:

- The contribution of patient neuropsychiatric symptoms and personality changes to carer distress may outweigh the burden posed by physical symptoms. Patient personality changes can lead to social isolation that compounds distress.

Needs of children

Although parents often feel tempted to avoid discussion about the seriousness of the condition[62] there is evidence that avoidance of discussion about parental cancer compounds distress in children[63]. The Cancer Council NSW has developed a resource for parents to guide them in discussions with their children about cancer: 'When a parent has cancer: how to talk to your kids'.[64] This resource provides suggestions about strategies for discussion with children, including practical examples specific to different developmental stages.

Recommendation	Level	References
Patients and their families should be informed that in general, talking about their feelings improves adjustment.	II	58

12.6 Psychosocial interventions

Internationally, it is recognised that patients with cancer should have access to psychosocial care in the context of a multidisciplinary team.[65] In a review of quality of life in patients treated for brain tumours, Heimans and Taphoorn[66] emphasise the importance of involvement of a multidisciplinary team in management, including access to psychosocial services. There is little literature describing

rigorously evaluated psychosocial interventions specific to patients with brain tumours, however in the general cancer population, there is high-level evidence of the benefits of psychosocial interventions, as indicated in Table 12.2 below.

Table 12.2 Psychosocial interventions and their impact on patients with cancer

Type	Description/benefits	Level of evidence
Cognitive behavioural therapy	Teaches skills in problem-solving, reframing attitudes, for example, challenging 'black and white' thinking, coping with stress and anxiety. Relaxation therapy, guided imagery or cognitive skills might be used to deal with stressful situations such as particular treatments, or to reduce nausea associated with chemotherapy. Improvement in emotional distress, coping, anxiety, depression and psychiatric morbidity.	Level I [67,68] Level II [45,69]
Supportive psychotherapy	Encourages the expression of emotion; validates the experiences of the individual and offers support through empathic listening, encouragement, and provision of information. Reflects on the strengths of the individual and encourages use of adaptive coping techniques. Improvement in mood, coping, and physical and functional adjustment.	Level I [67,68]
Group therapy	Places emphasis on sharing of experiences among patients with comparable disease. Participants feel that their experiences are validated, and that they can contribute in a meaningful way to the wellbeing of other members of the group. Improvement in mood, coping and adjustment, anxiety and depression.	Level I [70]

Adapted from *Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer* 2003. Reproduced with permission.[44]

Experienced clinicians highlight the importance of empathy and support, and the provision of information about coping with specific problems, including attention to symptom control.[56] Family members also may find it helpful to be given practical information such as the fact that singing and whispering may be intact in patients who cannot speak normally.[56]

The role of specialist oncology nurses is well established in some areas, and initial assessment of the role of a specialist neuro-oncology nurse suggests a potential role in provision of information and support, and in maintaining continuity of care for patients and their families.[71] Given the practical difficulties experienced by patients who may be unable to drive, different models of follow-up have been explored. One study examined telephone consultation follow-up conducted by an oncology nurse. Patients were generally satisfied with this method of follow-up, although the authors noted the tendency of patients to downplay symptoms, and this may be a disadvantage if carers feel that they are not as actively involved in follow-up.[72]

Support groups can be helpful through a number of mechanisms, including validation of the patient's experience and provision of the opportunity for patients to express their worst fears while also hearing about coping strategies of others.[5] Carers and patients may cope through reappraising and redefining their situation, and believing in their own personal strength.[54]

However for many patients and their families there remains a gap between perceived psychosocial needs and the support offered within clinical services.[73] This is consistent with a study of 12 patients and relatives two years after diagnosis of glioma, in which only one patient was able to resume work comparable to that undertaken prior to the diagnosis, but none of the patients had been referred for rehabilitation.[57]

Recommendation	Level	References
Patients and their carers should be asked about their emotional adjustment and given information about available support groups and specialist services, as these have been demonstrated to be effective in reducing distress.	I	45,66,67

12.6.1 Referral for specialist care

Patients or family members experiencing significant psychological distress or who have severe symptoms impacting on quality of life may benefit from referral for specialist interventions. Early referral may reduce the risk of developing significant psychological distress.[70] Appropriately trained social workers, psychologists or psychiatrists can offer a variety of effective treatments ranging from provision of information and support to cognitive behaviour therapy or pharmacotherapy.

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13 REHABILITATION

Brain tumour patients commonly experience changes in function and life quality during the course of their disease. The most common deficits include impaired cognition (80% of patients), weakness (78%), visual and perceptual deficit (53%), sensory loss (38%), and bowel and bladder dysfunction (37%).[1] While the traditional measures of clinical care tend to focus on direct tumour-related outcomes (morbidity, survival time, histopathology, imaging and laboratory data, and side effects of oncology treatments), rehabilitation therapies and outcome measurements offer a more functional approach that focuses on the total impact of treatments on the patient's life and social participation.

In general, patients with brain tumours (including gliomas) in the post-acute care stage respond to rehabilitation therapies in much the same way as patients with other more 'benign' neurological problems.

13.1 Description of rehabilitation environment

The standard rehabilitation care environment is multidisciplinary, with an appropriate range of medical, nursing and allied health professionals available and supervision of patient care by a medical specialist in rehabilitation medicine. Rehabilitation nurse specialists support patients and their carers by integrating care programs with the application of skills learned in therapy sessions at other times, in ward and other non-hospital settings.

Treatment roles of major individual therapy groups are defined, with areas of cooperative overlap. Physiotherapists primarily focus on impairments of an individual's motor function, strength and coordination, and their balance and mobility. Occupational therapists focus on second order self-care: the problems of function arising from patients' impairments as they restrict the individual's daily personal and independent living activities, and assessment of both the individual and their care environment. The main focus of speech pathologists is therapy for swallowing, communication and verbal interaction, and memory problems, with appropriate support from psychologists and social workers.

13.2 Common rehabilitation problems

Weakness was the second most common deficit reported in patients with brain tumours.[1] Muscle weakness may be related to an isolated limb weakness, hemiparesis, steroid-induced myopathy or other neurological impairment, for example, ataxic hemiparesis.[2] It may also be associated with sensory loss, cranial nerve palsy, dysarthria, dysphagia, aphasia, ataxia, diplopia and general debilitation. Symptoms will depend on the size, location and type of the brain tumour.[3]

Neurological impairment resulting in functional decline can affect bed mobility, ambulation, transferring from sitting or lying to standing, and activities of daily living (dressing, bathing, toileting). All these deficits can benefit from rehabilitation. The same principles of neuro-rehabilitation applied to persons with traumatic brain injury and stroke are appropriate for patients with brain tumours. Given the likelihood of progressive decline, flexibility in approach and frequent reassessments are required.[4,5] Studies addressing early stages of brain tumours (and metastatic tumours) have shown that brain tumour patients can achieve functional gains and rates of discharge comparable to those of patients with stroke, and have a shorter hospital stay.[6–8]

The physiotherapist, occupational therapist, speech pathologist and dietician need to assess the functional status of the patient to identify whether it would be safe to discharge the patient home. If unsafe, the social worker could assist in finding alternative discharge options for the patient. It may be advisable that the patient be assessed and educated regarding driving (*see section 13.5.5*). A combined approach between all members of the multidisciplinary team is essential for good patient management.

Recommendation	Level	References
Brain tumour patients should receive neuro-rehabilitation and can achieve functional gains and rates of discharge comparable to those of patients with stroke with a shorter hospital stay.	III	5,7

The management of neurological muscle weakness includes range-of-motion exercises, strengthening exercises, neuromuscular facilitation techniques and functional electrical stimulation. Specific aids may be prescribed by the consultant in rehabilitation medicine, for example, an ankle foot orthosis to improve gait.[5] Modified devices for walking may be recommended, including wide-based quad-sticks, standard walkers and hemi-walkers to increase the base of support and decrease the risk of falls.

A multidisciplinary approach is especially important in the management of hemi-spatial neglect, where rehabilitation programs involving occupational therapists and physiotherapists should be considered.[5] Exercise for cardiovascular conditioning and resistance training enhances the strength and endurance of preserved muscle groups. Cancer patients have the potential to improve from rehabilitation, but the timing, intensity and pace of activity must be in accordance with patient's goals and status.[9] Appropriate equipment such as mobility aids, commodes, dressing and bath devices are prescribed by the occupational therapist and physiotherapist.[10] Home modifications such as ramps and rails provide additional safety and independence in the home. Family, and training and education, are also important.

Cranial nerve damage may result in speech and swallowing dysfunction, optic neuropathy, ocular muscle paresis, trigeminal neuropathy, facial weakness and/or hearing loss. Referral to a speech pathologist will ensure training in techniques to prevent aspiration such as neck flexion, glottic adduction exercises, turning the head towards the weak side, breath-holding during swallowing, the selection of appropriate swallowing consistencies, and postural adjustments. Strategies to improve quality of speech include pacing, proper breath support and over-articulation. A modified barium swallow examination will assist in selecting the safest strategies for dysphagia.[9,10]

When managing ataxia secondary to cerebellar dysfunction, the application of weights to assistive devices and/or extremities may improve stability for severely affected patients. Safety awareness and measures to ensure an adequate base of support (eg walking aids) during motor activity are important educational strategies. Strengthening unaffected motor groups with resistive exercises helps compensate for impaired coordination.[9,10]

Compensatory techniques, the provision of assistive and orthotic devices, and exercise to enhance patients' preserved proprioception are recommended in the management of sensory dysfunction. Occupational therapists will encourage patients to engage in fine motor skills required for self care. Reliance on visual rather than tactile feedback is stressed. Unaffected motor groups are strengthened with resistive exercises to help compensate for impaired coordination. Upper extremities must be carefully positioned so as to reduce contractures, shoulder subluxation, pain and spasticity. Oedema management will help prevent chronic pain and assist in motor recovery. The use of elevation and/or washable spandex gloves or coban wraps, and compression stockings and massage is recommended.[9,10]

Steroid-induced myopathy is characterised clinically by proximal muscle weakness and eventual muscle wasting, especially in the pelvic girdle. One of the most frequent complaints is an inability to arise from the seated position. The myopathy can progress to involve the arms and neck. Evaluation of neck and hip flexor strength is required.[11,12] Respiratory muscles may also be affected, resulting in symptomatic dyspnoea.[13] Treatment is dependent on the reduction or discontinuation of steroids (if possible) plus physiotherapy, occupational therapy and a high-protein diet.[13]

13.3 Rehabilitation outcome measurements

Two measures of rehabilitation outcomes are commonly used. The older and simpler scale is the Barthel Index[14], which focuses on personal activities of daily living and basic mobility functions. Items are added to produce a score between 0 and 100; better scores show increased independence. Excellent internal consistency has been shown[15], with good inter-rater and test-retest reliability.[16]

The current standard scale for rehabilitation outcomes assessment is the FIM™ (Functional Independence Measure[17]), which is an 18-item instrument, each item being rated from 1 (complete dependence) to 7 (independence). The items are grouped to evaluate various aspects of motor function (transfers, walking, stairs, bowel and bladder control), activities of daily living (ADL) function (eating, grooming, bathing, dressing, toileting), and cognitive-communication function (speech communication, social interaction, problem-solving, memory). Full-scale scores thus range from 18 to 126. The three functional groupings approximately correspond to various areas of therapy, as described above. The scale has excellent internal consistency[18], and excellent inter-rater and test–retest reliability.[19]

13.4 Rehabilitation outcomes for brain tumour patients

Review of the literature found no randomised control trials of outcomes of rehabilitation therapy for disability in individuals with diagnosis of glioma, or of brain tumours more generally.

Seven observational studies[1,7,20–24] describe the rehabilitation of individuals having disability associated with brain tumours, including gliomas. Four studies[1,20-22] are non-comparative, and three[7,23,24] compare outcomes of therapy in brain tumour patients with brain trauma or stroke patients. All seven studies show improvement in patients' functional status during the course of rehabilitation therapy, using the FIM™.

Of the four non-comparative studies, only Marciniak et al[20] analysed the relationship of tumour histology with outcomes of rehabilitation, and they separately group and compare Grade III and IV astrocytomas with other tumour categories (meningiomas, brain secondaries, other brain malignancies). They found no difference in average length of stay or change in functional outcome between primary brain tumours and other tumour categories.

Mukand et al[1] describe therapy program results for patients with brain tumours, employing the FIM™ as a single domain. Three other studies divide the FIM™ into two domains: a motor function ADL domain and a cognitive-communication domain.[20–22] In addition, Garrard et al[22] separately measure ADL function using the Barthel score.

Three studies using the FIM™ describe similar improvements in functional status in patients with brain tumours, in comparison with rehabilitation outcomes for brain trauma patients[7,23] and for stroke patient.[24]

While there is no evidence relating neuropsychological intervention to functional outcomes in brain tumour patients, cognitive impairment related either to disease or treatment will clearly affect ability to participate in rehabilitation programs, as well as quality of life. Observational studies describe the place of formal assessment of cognitive impairment after treatment of brain tumours.[25–27]

There are two comprehensive reviews[6,28] of rehabilitation therapy in individuals with brain tumours that suggest that rehabilitation should be offered to patients with glioma.

Return to driving a motor vehicle after treatment for brain tumour is covered by national guidelines with regulatory force, in all Australian jurisdictions (see 13.5.5 below).[29]

13.5 Recovery outcomes of therapy for specific problems in patients with brain tumours

13.5.1 Association of rehabilitation therapy with improved motor/mobility function in patients with brain tumours

There is level III evidence that participation in a rehabilitation program is associated with improved performance of mobility function in patients with brain tumours[21,22] and at a rate comparable to improvement seen with rehabilitation therapy of motor function in benign neurological diagnoses.[6,23,24] While the gains in motor function are slightly less for high-grade gliomas, these patients nevertheless improve with therapy, and with an improvement rate similar to other brain tumour groups.[20]

Specific physiotherapy interventions which promote recovery of hemiplegic lower limb function are described in a case series which includes two brain tumour patients.[30]

13.5.2 Association of rehabilitation therapy with improved daily living functional ability in patients with brain tumours

There is level III evidence that participation in a rehabilitation program is associated with improved performance of personal activities of daily living, in patients with brain tumours.[22]

13.5.3 Association of rehabilitation therapy with improved cognitive-communication function and swallowing function in patients with brain tumours

There is level III evidence that participation in a rehabilitation program is associated with improvement in cognitive-communication function in patients with high-grade gliomas,[20] with an efficiency rate similar to other brain tumour groups.

There is no evidence for the use of speech therapy in managing swallowing disorders due to brain tumours but speech therapy may assist with residual problems related to swallowing, communication and cognitive function.

13.5.4 Association of neuropsychological intervention with improved outcomes in patients with brain tumours

There is no evidence relating neuropsychological interventions to outcomes in therapy programs for brain tumour patients. Observational evidence does however support neuropsychological evaluation of cognitive impairment after treatment of brain tumours.[26,27,31]

13.5.5 Criteria to indicate a possible safe return to driving after brain tumour treatment

National guidelines have been published,[29] with regulatory force in all Australian jurisdictions.

If a person has evidence of residual malignant brain tumour, or persisting hemianopia, quadrantanopia or diplopia, or uncontrolled epilepsy or impaired judgement after treatment of a brain tumour, they do not satisfy the criteria relevant to a diagnosis of glioma, for holding any commercial driver's licence, or an unrestricted private driver's licence.

Formal functional assessment, by a rehabilitation service, of the balance between demonstrated residual disability and the skills necessary to drive a motor vehicle is the best way to manage potential risks associated with brain tumour patients who expect to return to driving a car as part of their normal daily activities. This may involve medical, ophthalmological, psychological and occupational therapy assessments. It may occur in both off-road and on-road settings.

This will lead to determination: that the person is not safe to drive at all; or is safe to drive with some restrictions; or is safe to drive an adapted vehicle; or may drive without restriction. Recommendations are then made to the relevant driver licensing authority for its determination and appropriate endorsement of the person's driving licence. It is incumbent on the person to obey the determination of the driver licensing authority.

Recommendation	Level	References
Patients having residual problems after treatment of a glioma, with stable medical status, should be referred to a rehabilitation service with a range of medical, nursing and allied health professionals for multidisciplinary assessment and appropriate therapy and support of their problems, involving both the patient and their carers.	III	7–11,18
Physiotherapy should be offered to those glioma patients with residual problems in motor function, strength, and coordination, or balance and gait problems.	III	9,10,20
Occupational therapy should be offered to those glioma patients with residual problems in personal care and independent activities of daily living. As well as treating individual needs, therapy should also address the person's social and physical environment of care, and be supported by social worker intervention.	III	10
Therapy by a speech pathologist should be offered to those glioma patients with residual problems related to swallowing, communication and cognitive function. Where the services are available, this should be supported by assessment and intervention by a clinical psychologist or a neuropsychologist.	III	7
Glioma patients expecting to return to driving after treatment of their tumour should be referred to a rehabilitation service for full assessment of their ability to drive safely. Any resulting determinations of the driver licensing authority must be observed. For those who can return to driving, regular ongoing follow-up by the rehabilitation service is indicated, to review and manage any continuing risk associated with driving. Those who continue to drive unsafely, contrary to advice and the determinations of the driver licensing authority, should be counselled about the need to behave responsibly and the advice of the authority be sought, if they still continue to drive. In some situations, cancellation of the driver's licence may be necessary.	I	19

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14 FOLLOW-UP

14.1 General approach

The aim of follow-up for patients with either low- or high-grade astrocytoma is to evaluate tumour control, monitor and manage symptoms from tumour and treatment, and provide psychological support for the patient and their family.

The optimal frequency of follow-up visits is unknown and should be determined by the patient's clinical condition. However, a routine follow-up schedule of one to three monthly check-ups for patients with high-grade astrocytoma and three to six monthly visits for patients with low-grade astrocytoma would appear reasonable. The exact schedule will vary according to the patient's condition.

It is suggested that follow-up be undertaken in a setting where the patient has access to members of the multi-disciplinary team involved in their care. The team should include the treating specialists, neurologists, social workers, nurses, radiologists, physiotherapy, occupational therapy rehabilitation and palliative care specialists. A point of contact should be explicit. The lead physician may change over time depending on the patient's therapeutic needs. The general practitioner (GP) will also be involved in patient care but because gliomas are uncommon the GP's experience of gliomas will be limited and they are usually reluctant to be involved in tumour-specific follow-up.

While there are no high-level data that examine the benefits of care coordination, care coordination has become routine for most tumour sites. Brain tumour patients have a complex and difficult clinical course that involves multiple specialist clinical groups and repeated investigations. Care coordination is likely to significantly reduce the burden on patients and their carers.

There are many issues that need consideration during the follow-up of glioma patients including dexamethasone and anticonvulsant dosage, rehabilitation, driving, imaging frequency, palliative and pastoral care. They are discussed briefly below because other chapters in these guidelines provide detailed information.

Dexamethasone dose should be gradually reduced and ceased when possible. Dexamethasone should not be ceased suddenly because severe and sometimes catastrophic cerebral oedema can result. It may mimic tumour progression clinically and radiologically but can be rapidly reversed by the reintroduction of dexamethasone. Dose reduction should be titrated to patient symptoms. It may take up to one week for a reduction in dexamethasone dose to result in cerebral oedema so the titration must be undertaken slowly. Patients should be monitored for symptoms of the common side effects of dexamethasone such as high blood sugar, osteoporosis, proximal myopathy and gastric erosions (*see Chapter 11 Symptom management and complications).*

Anticonvulsants should only be ceased after consultation with a neurologist. Patients should have a prolonged period without a seizure, stable disease and a normal EEG. Medications should be slowly withdrawn over a period of months (*see Chapter 11 Symptom management and complications*).

Patients with brain tumours are only legally allowed to drive if they have no evidence of active tumour and are seizure free. This is unusual in patients with grade IV gliomas. Cognitive changes that are not readily apparent in a clinical consultation may severely impede safe driving. It is recommended that all patients are assessed by a rehabilitation physician and occupational therapist before being certified as safe to drive (*see Chapter 13 Rehabilitation*).

Follow-up imaging and interpretation is discussed in the next section. (For palliative and pastoral care see *Chapter 15 Palliative care*).

Key points:

- The aim of follow-up for patients is to evaluate tumour control, monitor and manage symptoms from tumour and treatment, and provide psychological support.
- The optimal frequency of follow-up visits is unknown and should be determined by the patient's clinical condition.
- Follow-up should be undertaken in a setting where the patient has access to members of the multi-disciplinary team.
- Dexamethasone dose should be gradually reduced and ceased when possible.

14.2 High-grade gliomas—imaging after surgery

14.2.1 Modalities to define tumour recurrence

Gadolinium enhanced MRI

Gadolinium enhanced MRI (Gd-MRI) is the imaging standard of reference for all intracranial neoplasms and is hence the preferred modality of choice except in the presence of contraindications such as a pacemaker.

There are no current standardised guidelines for either the timing or frequency of post-treatment imaging studies. The pre-operative study should have sufficient sequence variety to enable comparison and determination of interval change with the initial post-operative study, such as changes related to the surgery, like infarction. For example, the pre-operative imaging should include a T1-weighted sequence (pre and post contrast) and a T2-weighted sequence (preferably FLAIR – fluid attenuated inversion recovery).

Post-operative pre-contrast and post-contrast images should be obtained within 24 hours of surgery. These are best obtained with the same slice placement orientation as the pre-operative study and should also contain FLAIR, T1 pre and post contrast and diffusion-weighted imaging (to detect surgery-related infarction). This early study may determine the extent of resection with minimal confounding factor influence.

Follow-up surveillance MRI frequency thereafter will be influenced by extent of residual disease, different adjunctive therapy regimens, clinical trial enrolment, onset of new symptoms, patient compliance, and health status. Serial imaging at two to three month intervals is often used.

The definition of tumour progression on Gd-MRI has not been standardised and has been variously suggested as a 25% increase in the cross-sectional area of the tumour in the slice with the greatest amount of tumour, or as a 25% increase in contrast-enhancing volume. Recurrence has also been defined as a greater-than 50% growth in the time between two successive imaging studies. Progression may, however, occur at some distance from the original resection site in up to 10% of patients.[1,2] It may be difficult to determine progression because of 'pseudo-progression', which may be seen in up to 50% of cases after radiotherapy and chemotherapy.

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) is becoming more readily available and is useful in the follow-up of high-grade gliomas that have undergone radiation therapy when radiation necrosis is a significant possibility. Multi-voxel technique is strongly preferred because it gives a more representative sample. MRS is able to more accurately distinguish between tumour recurrence and radiation necrosis (which are essentially indistinguishable on conventional MRI). MRS of tumour recurrence demonstrates elevated choline/NAA and choline/creatinine ratios with choline to

contralateral choline ratios >1, although the precise cut-off values used in the literature have varied. Lactate peaks may indicate necrosis. Areas of mixed necrosis and neoplasm are however not uncommon and in these regions the spectral patterns are often less definitive. Thus, MR spectroscopy limitations exist and other non-invasive techniques (see below) may be employed.[3–28]

Perfusion MR

Perfusion MR (pMRI) or dynamic susceptibility contrast-enhanced MR may also be obtained in the same imaging sitting as Gd-MRI and MRS. pMRI has been shown to enable earlier distinction of responders to therapy than conventional MRI. In addition, it may be used to distinguish radiation necrosis and tumour recurrence, with tumour recurrence typically having an elevated relative CBV (cerebral blood volume), although once again methods of calculation and cut-off values vary in the literature[7,14,15,29–36]

Permeability MR

Permeability MR is not generally clinically available at present and hence does not have a significant role.

Diffusion-weighted imaging

Diffusion-weighted imaging with estimation of apparent diffusion coefficients (ADC) has demonstrated promise in improving the distinction of radiation necrosis and tumour recurrence and currently plays an adjunct role to Gd-MRI, MRS and pMRI. Tumour recurrence generally displays reduced diffusion due to cellularity. Diffusion tensor imaging (DTI) is a relatively new technique that in early studies has also demonstrated promise in this distinction.[24,25,37–47]

Positron emission tomography

Flurodeoxy-glucose (FDG)-positron emission tomography (PET) remains a useful tool in the follow-up of high-grade gliomas, however its use is largely confined to attempting to distinguish between radiation necrosis and tumour recurrence when other MR methods have proven inconclusive. Other PET tracers are largely experimental. In the event that Gd-MRI is not conclusive for recurrence, FDG-PET may be considered an appropriate 'problem-solving' evaluation.[2,15,48–99]

Single photon emission computed tomography

Single photon emission computed tomography (SPECT) is more readily available than PET and much cheaper. Of the radionuclides used, Thallium-201 and Technecium-99m Sestamibi are probably the most successful and most readily available SPECT tracers used for the differentiation of radiation necrosis and tumour recurrence. These tracers have a relatively high specificity, lower cost but poorer spatial resolution compared to PET.[40,44,62,63,66,67,75–77,83,87,94,100–111]

A comprehensive imaging practice might routinely include Gadolinium enhanced MRI, MRS, perfusion MR and diffusion-weighted imaging. The interpretation is based around FIVE parameters including: extent of T2 hyperintensity (best appreciated on FLAIR), contrast-enhancing volume, lesion ADC, lesion rCBV and spectral data.

The radiological changes of glioma progression include:

- increased extent of T2 signal abnormality
- increased enhancing volume
- elevated rCBV (eg approximately cortex or higher and increasing on serial studies)
- elevated choline/creatinine (eg >2), elevated choline to NAA and choline to contralateral normal >1 with an increase in these values on serial studies, and/or low ADC.

For a diagnosis of recurrent high-grade glioma there should be concordance of three or more of the above radiological changes.

14.3 Low-grade gliomas—imaging after surgery

14.3.1 Modalities to define tumour recurrence

MRI gadolinium enhanced

MRI gadolinium enhanced (Gd-MRI) is the imaging standard of reference for all intracranial neoplasms and is hence the preferred modality of choice except in the presence of contraindications such as a pacemaker.

There are no current standardised guidelines for either the timing or frequency of post-treatment imaging studies. The pre-operative study should have sufficient sequence variety to enable comparison and determination of interval change with the initial post-operative study (ie change related to the surgery, such as infarction). For example, the pre-operative imaging should include a T1-weighted sequence (pre and post contrast) and a T2-weighted sequence (preferably FLAIR).

Post-operative pre-contrast and post-contrast images should be obtained within 24 hours of surgery. These are best obtained with the same slice placement orientation as the pre-operative study and should also contain FLAIR, T1 pre- and post-contrast and diffusion-weighted imaging (to detect surgery-related infarction). This early study may determine the extent of resection with minimal confounding factor influence.

Follow-up surveillance MRI frequency thereafter will be influenced by the extent of residual disease, different adjunctive therapy regimens, clinical trial enrolment, onset of new symptoms, patient compliance, and health status. Serial imaging at three-month intervals initially is often used and the time interval generally gradually increased if there is no detectable change on serial imaging investigations.

The definition of tumour progression in LGG has not been standardised. MRI changes that indicate progression include increase in size and the presence of new lesions. The development of contrast enhancement or necrosis may indicate transformation to higher-grade glioma. Changes in the amount of T2 signal may be due to tumour progression or to post-treatment oedema.

Other MRI modalities

MRS is becoming more readily available and may be useful in the follow-up of low-grade gliomas that have undergone radiation therapy such that radiation necrosis is a significant possibility. Perfusion MRI has recently been shown to correlate with outcome in LGGs and hence may be a useful adjunct to the follow-up of these lesions.[112–114] Permeability MR is not generally available. ADC map evaluation and diffusion tensor imaging (DTI) do not appear to have particular practical value in the follow-up of LGGs at present.[42]

Nuclear medicine imaging

PET evaluation in the follow-up imaging of LGGs has not developed into a clinical tool at present.[115–118] SPECT evaluation in the follow-up of LGGs has not developed into a useful clinical tool at present.[118]

14.3.2 Interpretation criteria—low-grade transformation to higher-grade

Progression is expected to show:

- increased extent of T2 signal abnormality
- increased enhancing volume or development thereof

- elevated rCBV (eg approximately cortex or higher and increasing on serial studies)
- elevated choline/creatinine (eg >2), elevated choline to NAA and choline to contralateral normal >1, with increase in these values on serial studies.

It should be noted that oligodendrogliomas may demonstrate high-grade features on multiple parameters such as perfusion, spectroscopy, but may not be high grade.

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15 PALLIATIVE CARE

Despite recent advances in diagnosis and treatment, primary brain tumours remain incurable for the majority of patients. These patients have significant symptoms and concerns, posing considerable burdens on relatives, carers and health professionals. Given the relatively short life expectancy of these patients and the extent of their neurological debility, palliative care may be a significant component of management.

15.1 General

This section has been modified from the Australian Cancer Network *Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer*[1] according to the needs of brain tumour patients.

Palliative care has been defined as coordinated medical, nursing and allied services for people with life-limiting disease, delivered where possible in the environment of the person's choice, and which provides physical, psychological, emotional and spiritual support for patients and for patients' families and friends. The provision of hospice and palliative care services includes grief and bereavement support for the family and other carers during the life of the patient and continuing after death.[2] A palliative approach involving attention to symptom control and the psychological, social and spiritual wellbeing of the patient and their family is relevant at all stages of the disease, and especially in the terminal phase. Although focussing on quality of life, palliative care is also concerned with the quality of dying.

Palliative care utilises advance planning rather than crisis intervention. It offers a multidisciplinary model of care that is focused on the whole person within their social and emotional context, rather than just the disease. However, a good knowledge of the natural history of the disease and relevant oncological practice is essential for good quality palliative care.[3]

The Palliative Care Australia Standards for providing quality palliative care in any setting are listed in Table 15.1.

Table 15.1 National Standards for the provision of quality palliative care (abridged)[4]

1.	Care, decision-making and care planning are based on a respect for the uniqueness of the patient, their caregiver and family.
2.	The holistic needs of the patient, their caregiver, and family are acknowledged in the assessment and care planning processes and strategies are developed to address those needs.
3.	Ongoing and comprehensive assessment and care planning are undertaken to meet the needs of the patient, their caregiver and family.
4.	Care is coordinated to minimise the burden on patient, their caregiver/s and family.
5.	The primary caregiver is provided with information, support and guidance about their role according to their needs and wishes.
6.	The unique needs of the dying patients are considered, their comfort maximised and their dignity preserved.
7.	The service has an appropriate philosophy, values, culture, structure and environment for the provision of competent and compassionate palliative care.
8.	The patient, their caregivers and family have access to bereavement care, information and support services.
9.	Community capacity to respond to the needs of people who have a life-limiting illness is built through effective collaboration and partnerships.
10.	Access to palliative care is available for all people based on clinical need and is independent of diagnosis, age, cultural background or geography.
11.	The service is committed to quality improvement and research in clinical and management practices.
12.	Staff and volunteers are appropriately qualified for the level of service offered and demonstrate ongoing participation in continuing professional development.
13.	Staff and volunteers reflect on practice and initiate and maintain effective self-care strategies.

15.2 Specialist versus generalist palliative care

The National Strategy for Palliative Care encourages the use of existing networks and community services in conjunction with palliative care specialists to deliver palliative care.[5] All clinicians have a responsibility to be proficient in basic palliative care. Most palliative care will be provided by the existing network of carers, coordinated by either the general practitioner or treating physician or oncologist. Referral to palliative care should not be limited to the end-of-life phase of illness. Difficult cases will benefit from referral to a specialist palliative care service. In metropolitan areas, specialist palliative care services are generally available both in hospital and in the community to provide expert symptom management and supportive care. This may be a consultative service or involve transfer of care to a palliative care physician. Access to specialist palliative care beds within hospitals or hospice units is usually available. Access is more limited in rural and remote areas. Consultations may be by telephone or video-conferencing and access to specialist inpatient care may be limited by distance. An evolving role is that of a specialist neuro-oncology nurse to provide support for patients newly diagnosed with a brain tumour as well as those with advanced disease.

As the availability of specialist palliative care increases, specialist palliative care teams should be utilised to achieve optimum outcomes for the patient with brain tumours, particularly when treating complex or difficult issues. The involvement of a specialist palliative care team in the care of patients with cancer in general increases patient and carer satisfaction, increases the amount of time spent at home by patients, reduces the time spent in hospital, reduces the overall cost of care and increases the likelihood of the patient dying where they wish.[6,7]

Recommendation	Level	References
Specialist palliative care services can improve outcomes in the care of patients with cancer and should be available for all appropriate patients.	I	6,7,8

Key point:

- Referral to palliative care should not be limited to the end-of-life phase of illness.

15.3 Sites of palliative care

Palliative care emphasises that care is delivered where possible in the environment of the patient and carer's choice.[9] Good communication between health professionals is essential to ensure smooth transition from one site to another. It is important to be clear which health professional bears the primary responsibility for care in each setting. Continuity of care can be provided through clear communication between all health care providers and the patient and family so that accurate and detailed information about all aspects of the patient's condition, treatment and wishes is known.

15.3.1 Own residence

This refers to either the patient's own home, the home of another, a nursing home or hostel. Increasingly, staff in nursing homes and hostels are being called on to deliver palliative care where resources to care for a dying resident may be limited.[10,11]

The general practitioner will be the key medical practitioner in delivering palliative care at home, usually with the assistance of community nurses. The local palliative care service will usually be able to add the support of specialist palliative care nurses and a specialist palliative care physician as well as counsellors, pastoral care workers and volunteers. Links with other community services mean that assistance can be accessed for physiotherapy, nutritional support, occupational therapy and home help.[4]

If unnecessary hospital admissions are to be avoided, it is essential that the patient and family know who to call in the event of a crisis and have access to support 24 hours a day, seven days a week. The latter is not achievable in many areas. Although reliable data are limited, home-care programs that provide adequate support for the carers are generally assessed favourably.[12–15] Carers and relatives of terminally ill patients report more support was needed during care at home, particularly for activities of daily living and domestic chores.[16] Families undertaking home care experienced higher levels of stress and social disruption than those whose relatives were cared for in institutions.[17]

15.3.2 Acute hospital

Although several studies have pointed to patients' requests to die at home, this may reflect a wish that they never develop a problem that requires hospital admission. Even when no further curative treatment is anticipated, situations arise that will be best treated in an acute hospital. These include uncontrolled seizure activity, infection, carer fatigue or difficult symptom control. Brain tumour patients are likely to have had frequent contact with hospital staff and feel safe and secure there. A family caring for a patient at home may need respite for many reasons, and an acute hospital may be the only site available. As the illness progresses and the patient's strength and time are limited, hospital outpatient visits for review may become burdensome and should be minimised by liaison between the hospital specialist, the local palliative care team and the general practitioner.

Where patients wish to continue their direct links with a specialist physician or hospital team, an effective level of contact should be achieved with priority based on patient need, preference and convenience. Despite the availability of community based palliative care and hospices, many patients still die in acute care hospitals.[18] Attention to symptom control, psychological and emotional support for the patient and family, and agreement on the goals of care can allow death to occur peacefully in this setting (see *15.8 Care of the dying patient*).

15.3.3 Palliative care unit

Admission to a specialist palliative care unit or hospice bed may be required for symptom assessment and review of medications if new problems arise, or for terminal care. Admission for respite may be necessary for family and patient relief. Direct admission from an acute hospital may be indicated for patients with neurological impairment and symptom burden such that care in the community is not possible. This may be particularly so for patients suffering from severe neurological disabilities. A preference for inpatient palliative care rather than home care highlights the importance of having adequate palliative care beds available.[12]

15.4 Timing of referral

Early referral to a palliative care service will be facilitated if the palliative care health professionals are already an integral part of the multidisciplinary treatment team at the cancer centre or treating hospital.[19,20] It is not easy to determine prognosis and methods used to identify survival time have limitations in accuracy and precision and are therefore not routinely recommended for assessing the timing of referral to palliative care.[21,22] Referral to a palliative care service should be based on need, not on life expectancy,[23] but early referral to a palliative care team allows the establishment of access and contacts, and exploration of options for future care without the need for immediate decisions. Early referral will facilitate subsequent continuity of care between hospital, home and hospice and thus mitigate against any sense of abandonment.[24–26] General practitioners who continue to be involved in the ongoing care of the patient often initiate palliative care. The concept of parallel care, suggesting a close and continuing cooperation between oncological and palliative services throughout the course of the illness, is particularly logical for patients with brain tumours. The provision of active treatment and comfort measures and death preparation in parallel has been called the 'mixed management model' of end-of-life care.[27] The involvement of palliative care professionals does not preclude the continuation or commencement of chemotherapy, courses of radiotherapy, or surgical or other procedural interventions aimed at reducing tumour burden or relieving symptoms.[28] Such shared care models reduce concerns of abandonment on behalf of both the doctor and the patient. The provision of information about a palliative approach may help patients and their families to consider a palliative approach as active care rather than withdrawal of treatment.[29]

Recommendation	Level	References
Methods used to identify survival time have limitations in accuracy and precision and are therefore not routinely recommended for determining the timing of referral to palliative care.	I	21,22

15.5 Breaking bad news

Most patients from Western countries prefer some information regarding prognosis when first diagnosed with a life-limiting illness.[30] The amount of information given and the distress that this causes will vary from patient to patient. Most patients place great emphasis on their relationship with key health care professionals and prefer 'bad news' information to come from a confident expert.[31] Evidence-based clinical practice guidelines for communicating prognosis and end-of-life issues with

adults in the advanced stages of a life-limiting illness, and their caregivers, have been published.[31] Specific palliative care question prompt lists are also available to help advanced cancer patients and their caregivers ask appropriate questions about likely outcomes and the intention of treatment.[32] *Chapter 2 Approach to the patient* contains more information on breaking bad news.

Recommendation	Level	References
All patients with advanced progressive life-limiting disease should be given the opportunity to discuss prognosis and end-of-life issues.	IV	33

15.6 Symptom management at the end of life

People with brain tumours experience a wide variety of symptoms. The most common physical symptoms are fatigue, decreased ability to concentrate and remember, loss of independence, nausea, and pain.[34] Added to this are problems relating to neurological deficits and immobility.

The principles of symptom control, used as a standard by clinicians include:

- thorough assessment of the symptom, including understanding of the meaning ascribed to it by the patient
- explanation of the likely cause
- investigation be undertaken only if it will change the course of action to be followed
- institution of treatment based on the known or likely aetiology, available options for treatment and the wishes of the patient
- monitoring of the response to treatment and modification as necessary.

For guidelines on the management of symptoms, refer to *Therapeutic guidelines: palliative care*.[35]

15.6.1 Fatigue

Fatigue 'is a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning'.[36] It is the most common symptom experienced by patients with brain tumours.[34]

Assessment of fatigue starts by screening all patients. Some patients expect to feel tired and think that nothing can be done to improve this symptom. A comprehensive history, physical examination and limited investigations are needed to look for reversible factors. The pattern of fatigue may vary and how it is affecting function is perhaps the most important part of the history.

The causes of fatigue are usually multi-factorial, and the aim of the assessment is to identify potentially treatable contributors and to work out a management plan.

Table 15.2 Factors potentially contributing to fatigue

Contributing factor	Examples	Treatment options
Anaemia	anaemia of chronic disease	trial of blood transfusion
Pain	headache	analgesia management as per WHO guidelines[37]
Psychological	anxiety, depression, existential distress	psychosocial interventions such as support groups, stress management and relaxation. treatment of underlying psychological state
Symptom distress	dyspnoea, nausea and vomiting	treatment of symptom
Electrolyte disturbances	renal, hepatic, endocrine dysfunction (eg hypothyroidism, hyponatremia)	reversal of abnormality
Nutritional deficiency	anorexia/cachexia syndrome	dexamethasone megestrol acetate
Infection	urinary tract infections	antibiotics
Sleep disturbance	insomnia	sleeping tablets non-pharmacological approaches
Medications	sedatives, opioids, diuretics	review of medications
Deconditioning	decreased physical activity	energy conservation exercise optimisation of activities of daily living

As well as specific treatments related to treatable conditions, there are some general management strategies that can be helpful. These include education (especially of families, who need to acknowledge that fatigue is not the sole result of decreased food intake), energy conservation, exercise, optimisation of activities of daily living, psychosocial interventions (such as support groups, stress management and relaxation).[38,39]

There are few data about medications that can improve fatigue at the end of life. In general it has not been shown that any medications have a substantial impact on the symptom, and there is usually a risk of side effects. Corticosteroids and megestrol acetate have been shown to have a small beneficial effect in overall quality of life and fatigue.[40,41] Psychostimulants (methylphenidate, dexamphetamine), while showing some promise in non-randomised controlled trials, failed to show a benefit in the only randomised controlled trial, completed so far.[42] If a trial of medication is given it is important to review the benefits and side effects regularly to ensure their value in an individual situation.

Recommendation	Level	References
Medications (corticosteroids, megestrol acetate) may be trialled as a treatment of fatigue.	II	40,41
Psychostimulants are not recommended for fatigue, outside of clinical trials.	II	42
Psychosocial interventions and energy conservation may help with fatigue.	II	39

15.6.2 Headache

Brain tumour headache can be due to the effect of raised intracranial pressure on parts of the brain that are sensitive to pain, as well as to invasion of central pain pathways. About half of patients with brain tumours experience headache.[43] The most common characteristics of the headache in one case series was severe intensity, coming on over days to weeks, lasting hours, intermittent, occurring either in the morning or night, associated with nausea and vomiting, and throbbing in quality. The site of pain does not always correlate with the anatomy of the tumour and can even occur on the contralateral side.

The treatment of headache starts with decreasing oedema and intracranial pressure. Corticosteroids are the mainstay of treatment. The dose needs to be titrated to pain relief and side effects. It is optimal to use the lowest dose possible to try to avoid or minimise longer-term debilitating side effects that are often irreversible in this population. Simple analgesia with paracetamol or non-steroidal anti-inflammatories (NSAIDs) can also be used. Care must be taken when using NSAIDs in conjunction with steroids because of the potential for gastrointestinal side effects. If these measures fail to give pain relief, opioid analgesics should be used according to the WHO guidelines.[37] Opioids should be used early in those patients in whom the side-effects of steroids are already debilitating.

Assessment of headache and other pain can be difficult in patients who are unable to communicate. It requires careful assessment of the history of pain, as well as objective physical findings (eg rubbing head) that seem to improve with the administration of analgesics.

Recommendation	Level	References
Opioids are the analgesics of choice for moderate to severe cancer pain.	I	44

15.6.3 Seizures

Chapter 11 Symptom management and complications discusses the use of anticonvulsants in general. The main difficulty in treating seizures at the end of life is the administration of medication. Patients become drowsy as they deteriorate and their ability to swallow oral medications decreases. Moreover, they do not usually have cannulas in-situ for intravenous access. Coupled with this is the fact that the most common anti-epileptic medications (sodium valproate, carbamazepine and phenytoin) can only be delivered orally or intravenously. Patient who have never had a seizure should not be started on prophylactic anticonvulsants.[45]

Changing from oral to alternative routes for the administration of anticonvulsant medication (eg sublingual delivery) has not been well studied. Medications that have been used 'off licence' by alternate routes include clonazepam (sublingually or subcutaneously), midazolam (sublingually or subcutaneously) and diazepam (rectally).

Intractable seizures at the end of life

Status epilepticus can be defined as more than 30 minutes of continuous seizure activity, or two or more sequential seizures without recovery of full consciousness between the seizures.[46] The most common cause in the setting of a brain tumour is progression of disease, but it is important to consider other factors. These include cerebral haemorrhage, metabolic conditions (especially hypoglycaemia), medications and substance withdrawal (eg alcohol and benzodiazepines). The approach to treatment is dependent on the setting of care. Generally, intractable seizures at the end of life are managed in the home or in a palliative care inpatient facility. The main aim of treatment is to stop the seizure activity and maintain the quality of life for the patient and family (Table 15.3).[35,47] Phenobarbitone is recommended only when other medications have failed to control seizures. Propofol can only be delivered intravenously and requires close monitoring. It is not appropriate for use within the community setting. The effect of rectal diazepam is unpredictable due to inter-patient variation in absorption. It is important to communicate fully with the family and carers at all times, as seizures can be very distressing.

Table 15.3 Suggested treatment approach for intractable seizures at home or a palliative care unit

Benzodiazepines	diazepam 5–10mg rectally or 5–10mg IV at the rate of 5mg per minute midazolam 2.5–5mg subcutaneous injection clonazepam 1mg subcutaneous or 1mg by slow bolus intravenous injection followed by a continuous infusion of benzodiazepines
Phenytoin	15–20mg/kg IV, by slow bolus injection (maximum 50mg/minute)
Phenobarbitone	100–200mg subcutaneous or intramuscular injection followed by continuous subcutaneous infusion of 600–2400mg over 24 hours[48]
Propofol	Used if all other treatments have been unsuccessful. Expert advice should be sought.

Nausea and vomiting

Central nervous system tumours may directly or indirectly (through raised intracranial pressure) stimulate the emetic centre in the brain, leading to nausea and vomiting. If raised intracranial pressure is suspected, the initial treatment is usually with corticosteroids. Mannitol has been used in resistant cases. Failure to control nausea with this approach raises the possibility of other causes. The management in this situation depends on the likely mechanism and follows standard guidelines.[49] For nausea and vomiting not responding to usual medications, other drugs, for example, methotrimeprazine and cyclizine, can be accessed in hospitalised patients through the Special Access Scheme.

15.7 Special problems for patients with brain tumours

15.7.1 Feeding, fluids and dysphagia

The conscious state of a patient with a brain tumour will generally deteriorate during the terminal stage of the illness. This is typically associated with reduced appetite, reduced oral intake and varying degrees of dysphagia. There may be a risk of aspiration and pneumonia. Aspiration can be reduced by administering thickened fluids. During the final phase of life, a total inability to swallow is a normal phenomenon. Given this highly predictable sequence of clinical progression, it is essential that patients, families and carers are provided with accurate information about issues relating to feeding, nutrition and fluids. Often these issues can be emotive for families and decision-making can be difficult for both patients as well as the tending professionals.

It is important to emphasise to patients and families that nutritional support, either enterally or parenterally, does not improve morbidity or prolong survival in terminally ill patients.[50,51] Evidence-based guidelines have recommended that patients with post-coma unresponsiveness or a minimally responsive state should not be offered gastrostomy feeding.[52] Patients and families typically require reassurance that the anorexia associated with dying is not uncomfortable. When given this information, it is unusual for patients or families to request ongoing artificial nutrition in the setting of an advanced brain tumour. It is essential that the information being provided by all treating professionals is consistent.

The issue of hydration at the end of life is often controversial in cancer care[51,53]and in brain tumour patients it presents unique challenges. The critical challenge is to provide accurate clinical information and allow for patients or their decision-makers to make informed choices. A palliative approach to care emphasises that irrespective of the provision of artificial hydration, the patient should continue to receive high-quality nursing care with attention to pain relief and symptom control with meticulous attention to mouth care. In brain tumour patients, hydration can worsen the clinical condition due to increased cerebral oedema. However, if a patient has specific symptoms of unsafe swallowing but otherwise has a reasonably good functional status, there may be valid arguments to support parenteral or subcutaneous fluids until the patient's condition deteriorates to such an extent that this is no longer appropriate.

In the dying patient, the general consensus is that parenteral hydration is not beneficial.[43] Each case must be considered individually. Recognition of the strong emotional, cultural and spiritual biases of patients and professionals will assist in tackling this difficult issue. Good decision-making process is essential. One should not avoid the opportunity to engage with patients and their families and assist them in making ethical and evidence-based choices about nutrition and hydration.

Recommendation	Level	References
Artificial nutrition is not recommended in patients with advanced cancer because it does not reduce morbidity or mortality.	I	51
Meticulous attention must be given to mouth care in the dying patient.	IV	53

Key point:

- The issue of parenteral hydration in the dying patient remains controversial.

15.7.2 Cognitive dysfunction, depression and acute confusional state

Cognitive impairment is common in patients with brain tumours (70–80%)[54] and can profoundly interfere with work, family and carer relationships, quality of life and even personal identity.[55,56] They are discussed in detail in *Chapter 12 Psychosocial care*.

Treatment of primary brain tumours with surgery, radiotherapy and chemotherapy and/or adjunctive medications such as steroids, opioid analgesics, anticonvulsants, anti-emetics and anxiolytics can result in further negative effects on cognitive function.[57–59] Accurate assessment of cognitive impairment (including attention, memory, learning and information processing speeds, multi-tasking, visual-spatial ability, mood and personality) at the initial clinic visit and throughout the course of the illness is vital. Appropriate neuropsychological tools include the Neuro-behavioural Cognitive Status Examination[60] and the Addenbrooke's Cognitive Examination[61]. Treatment effects can be subtle and may not be captured by blunt measurement tools such as the Mini-Mental State Examination (MMSE). Most research to date on treatment effects has been focused on gross endpoint changes in

the MMSE rather than more subtle endpoints such as improvement in neurocognitive function (memory, verbal fluency, visual–motor speed, executive function, language and reasoning) or delays in neurocognitive progression.[62]

Improvements in prognosis in some patients following radiotherapy and chemotherapy has implications for palliative care and introduces the need for active early rehabilitation based on a clear assessment and proactive search for cognitive deficits according to tumour location[63] (see Table 15.4). See also *Chapter 13 Rehabilitation.*

Table 15.4 Cognitive deficits according to tumour location

Tumour site	Common deficits
Left hemisphere	Language, verbal memory and reasoning, right-sided strength and dexterity
Right hemisphere	Visual perception and construction, left hemi-spatial inattention, left-sided strength and dexterity
Anterior (frontal lobes)	Executive functions

There is increasing evidence that active rehabilitation in patients with brain tumours is as effective in the earlier phases of their disease as it is for patients post-stroke or traumatic brain injury.[54,64] Rehabilitation programmes have been based on multidisciplinary cognitive rehabilitation principles that include restoration (cognitive training, memory rehearsal, etc), substitution (compensatory devices and strategies), restructuring (changing expectations and environmental settings) and coping with personal identity crises (reminiscence therapy or psychotherapy groups centred on participant past narratives exploration).[55,65]

Several pharmacological interventions have been tried with variable success. These include psychostimulants, for example, methylphenidate for attention, cognitive processing speed and mood enhancement[66,67]; antipsychotics, for example, risperidone for behavioural disturbance[68]; and acetylcholinesterase inhibitors, for example, donepezil in irradiated brain tumour patients with possible deficits in neurocognitive processing.[69]

The management of elderly poor-prognosis patients remains a challenge. Comprehensive cognitive assessment at presentation is vital to establish a baseline and to provide adequate support. The use of steroids and mannitol to control peri-tumoural oedema combined with physiotherapy to maintain function may have a significant positive effect on quality of life.[70] New and more specific indicators, such as Quality Adjusted Survival Parameters, which are able to balance the benefits against the side effects of treatment are indicated for this elderly population.[71]

Not all impairment of cognitive function will be related to the primary disease. There are multiple other potential causes of impaired function in patients with brain tumours, for example, urinary tract infection, drug toxicity, substance withdrawal. Any potentially reversible cause should be actively sought and treated appropriately.

15.7.3 Bowel and bladder problems

Comprehensive bowel care commences with a detailed history of past and present bowel habit, instigation of a bowel chart and re-evaluation of current aperients. Bowel management for brain tumour patients may be complicated by the patient's reduced mobility, neurological deficits and inability to communicate. Carer and staff education in using equipment, for example, hoist and slings for transfer to commode or toilet, is essential. As well as having the patient in a sitting position, carers should ensure there is provision for privacy and safety.

Brain tumour patients are at increased risk of constipation due to reduced mobility and low oral intake secondary to dysphagia and/or drowsiness, as well as the medications they may be receiving (eg opioids, antidepressants), their reduced mobility and reduced oral fluid intake caused by dysphagia and/or drowsiness. Routine bowel management review is essential. A digital rectal examination plus physical examination and a plain film of the abdomen may be required to ascertain the site and degree of the constipation. Aperients should be reviewed regularly. Consider the use of a constipation flow-chart.[72] Faecal impaction is the accumulation of compacted faecal material in the rectum or colon. The patient may develop symptoms such as paradoxical diarrhoea with incontinence, anorexia, nausea and/or vomiting. They may also have urinary frequency, retention or overflow of urine.

The passage of some stool does not rule out the presence of faecal impaction. The management of faecal impaction requires 'per rectum' interventions (enemas or suppositories) as well as aperients. Abdominal x-ray may be required for diagnosis and may need to be repeated to ascertain the impact of management strategies. Manual evacuation is occasionally necessary; patients should have appropriate sedation prior to this procedure.

During the terminal phase, bowel evacuation in a drowsy, bed-bound patient should be regulated with suppositories prior to bed bath. The use of incontinence aids provides comfort and security for the patient.

Urinary incontinence, or the failure to control urine, may be due to many factors including retention with overflow or be associated with neurological dysfunction. The patient may have expressive dysphasia and therefore be unable to communicate the need for toileting or have reduced mobility resulting in urge incontinence.

Assessment of urinary incontinence includes history taking, physical examination, urinalysis and the elimination of other predisposing causes of incontinence including urinary tract infections and steroid-induced diabetes. Incontinence aids ranging from discrete panty liners to continence pants may be necessary. Condom drainage or catheterisation should be considered.

This may eliminate the incontinence but may not affect the sensation of urinary urgency. Patients with short-term memory loss, hemiplegia and urinary frequency or incontinence may experience multiple episodes of nocturia. This can be exceedingly difficult to manage. The patient will be at increased risk of falls and both patient and carer will experience sleep deprivation. Respite for carers may be indicated.

15.7.4 Pressure areas

The terms 'pressure sores', 'decubitus ulcers', 'bed sores', 'pressure necrosis' and 'ischaemic ulcers' describe any lesion caused by unrelieved pressure damaging underlying tissue.[72] The risk of any individual patient developing a pressure ulcer is assessed according to the Norton Risk Assessment or the Waterlow Pressure Sore Prevention/Treatment policy.[73] Some degree of impairment of skin integrity is almost inevitable in a bed-bound patient. Once present, pressure ulcers are very difficult to heal and can contribute significantly to the morbidity of a bed-bound patient. In the extreme, they are a constant source of pain and potential infection and can impose a significant burden on carers.

Predisposing risk factors in brain tumour patients are impaired mobility, sensory perception and inactivity. The patients are often Cushingoid and hemiparetic; this increases the risk of pressure ulcers caused by friction and shearing of skin tissue that can occur when repositioning patients.

Prevention of pressure ulcers is essential. Simple measures include turning every two hours, sheep-skin rugs and resting the heels on water-filled gloves. Referral of patients to the occupational therapist for assessment of equipment requirements is recommended. Once established, pressure ulcers can be difficult to heal, especially after long-term steroid use and immobility.

Ulcer management should be directed by a wound care management nurse or stomal-therapist if available. Patients may require a breakthrough dose of analgesia prior to dressing procedures. There is some evidence to support the use of topical opioids and local anaesthetic agents for chronic wound pain associated with dressing changes or debridement.[74]

Key point:

- Opioids applied topically (eg morphine paste or liquid) can relieve the pain associated with pressure area wound care.

15.7.5 Corticosteroid use

Steroids are used almost routinely in patients with primary brain tumours and have both specific and nonspecific indications.

- **Specific indications:** (*see Chapter 11 Symptom management and complications*) These relate to the palliation of symptoms associated with raised intracranial pressure. Oedema resulting from a breakdown in the normal blood–brain barrier in patients with brain tumours causes an increase in intracranial pressure and neurological dysfunction, presumably because of ischaemia from the mass effect. Associated symptoms include headache, nausea and vomiting and a decreased level of consciousness. Corticosteroids frequently lead to a rapid and substantial improvement in both neurological dysfunction and symptoms related to this peritumoural oedema. The exact mechanism for this is unknown.[75] Low-dose dexamethasone (4mg) has been shown to be as effective as 16mg in the palliation of symptoms of brain tumour oedema in patients with metastatic brain disease.[76] Higher doses may be needed for primary brain tumours.

- **Nonspecific indications:** steroids are used to palliate symptoms commonly associated with advanced malignant disease such as decreased appetite, pain, dyspnoea, low mood and general fatigue. Steroids have been shown to be similar to megestrol acetate with respect to appetite enhancement and non-fluid weight gain[77] and superior to placebo in controlling pain.[78] The evidence of benefit for all other nonspecific indications has not been tested in a controlled setting.

Dexamethasone is generally used in routine clinical practice because of its relative low mineralocorticoid and high glucocorticoid potency compared to other steroids. It may be administered orally or parenterally. The dose is individualised to the patient's needs and is usually given in the morning in an attempt to prevent insomnia. This is unlikely to protect against nocturnal agitation however, as the biological half-life of the drug is very long (36–54 hours).

The prolonged use of steroids must be balanced against the potential for side-effects (Table 15.5) that are related to dose and length of treatment.[79–82] Approximately one-half of patients treated with steroids over a prolonged period develop disturbed glucose metabolism that may persist following withdrawal of the drug.[83] The incidence of severe psychiatric illness is uncommon at low doses but increases to almost 20% of patients treated with more than 12mg/day dexamethasone.[84] Analyses of the magnitude of the risk of steroid-induced peptic ulcers provide conflicting results.[75] Most patients treated with conventional doses of steroids, (for example, 16mg of dexamethasone per day for more than 2–3 weeks) develop some degree of myopathy.[79] This can significantly hinder mobility and the ability to care for patients at home. Moreover, the benefit of steroids may diminish with time[85] either because of loss of effect of the drug or progression of disease.

Best practice is to reduce the dose slowly to the lowest effective dose and to monitor side effects continuously.[86] Benefit should be weighed against toxicity. Generalised dose schemes should not be used, but dosage should be adapted to each patient's individual needs.[87] Some advocate pulsed doses (a short course of moderate dose dexamethasone) rather than prolonged courses, to relieve symptoms and minimise side effects. The use of steroids at the end of life is controversial. Many clinicians discontinue the drug when the patient is no longer able to take tablets by mouth. Others continue to

deliver a tapering dose parenterally in an attempt to prevent symptoms of steroid withdrawal. The continued treatment with increasing doses of steroids in the terminal phase may serve only to prolong death rather than contribute to quality of life.

Key point:

- Patients should be maintained on the lowest possible effective steroid dose to minimise side effects.

Key points:

With regard to steroids the clinician should;

- Dose according to each patient's individual needs.
- Consider pulsed rather than continuous treatment.
- Monitor continuously for side effects.
- If no longer of benefit, wean down slowly and discontinue.
- Consider prophylactic nystatin and gastroprotection in all patients, especially those with added risk factors.

Table 15.5 Steroid side-effects

Cushingoid habitus—moon face, buffalo hump
Skin changes—striae, acne, tendency to bruising, skin frailty, poor wound healing
Proximal myopathy
Psychological disturbance—restlessness, agitation, anxiety, sleep disturbance, behavioural change, frank psychosis
Hyperglycaemia and glycosuria
Peripheral oedema
Gastrointestinal toxicity
Infections—oral candidiasis, increased susceptibility to infections

15.8 Care of the dying patient

The unique needs of dying patients must be considered, their comfort maximised and their dignity preserved. Palliative Care Australia Standards.[4]

Common themes contributing to a good death include control, autonomy and independence with respect to pain and symptom control, place of death, who should be present at the time of death and the maintenance of privacy. Access to information and expertise, as well as spiritual and emotional support, is also important.[88] The most important components of a good death, according to focus group work with health professionals, patients and carers, are good pain and symptom management, clear decision making, preparation for death, completion, contributing to others, and affirmation of the whole person.[89] Patients and families tend to fear 'bad' dying more than death itself. Attributes of a

'bad' death include the lack of opportunity to plan ahead and arrange personal affairs. Issues that contribute to the sub-optimal care of patients dying in hospital include a lack of open communication, difficulties in accurate prognostication and a lack of planning of end-of-life care.[90]

Hospice-type care is cited as the 'bench-mark' and should be available across all settings.[91]

Systems for managing end-of-life care and mortality management should be in place in all health institutions (Australian Council of Health Care Standards).[92]

Strategies that have been designed to improve end-of-life care include the increasing acceptance and use of advance care directives, the education of health care professionals in principles of 'dying well' and the development of integrated care pathways (ICPs) for the care of the dying.[91] These multidisciplinary care plans are patient-centred and address not only the physical but also the important psychosocial, spiritual and practical issues that surround death. They detail the essential goals necessary for the care of dying patient (Table 15.6) and empower non-specialist (generalist) palliative care workers in the palliative approach. An essential component of the pathway is a change of emphasis of care away from life-saving measures at all cost to the best supportive care of a dying patient.

Making a diagnosis of 'dying' is not always easy. Moreover, while it may be clear to relatives, carers and other health professionals that a patient is dying, the treating team may be loath to accept 'medical failure' and change the goals of care. The palliative care team may facilitate the change in emphasis. Typically, a patient who is entering the terminal phase is bed-bound and withdrawn, with increasing drowsiness, weakness and decreased mobility. Dying patients are unable to take food or fluids and may become restless, confused or 'terminally agitated'. Patients with advanced disease who deteriorate and appear to have entered a terminal phase may have an easily reversible cause for their deterioration, for example sepsis or opioid toxicity. A reversible cause is more likely if there has been a rapid deterioration from a previously good quality of life.

Table 15.6 Goals of care for patients in the dying phase[93]

Domain	Goal	
Comfort measures	1	Current medication assessed and non-essentials discontinued
	2	As-required subcutaneous drugs written up according to protocol (pain, agitation, respiratory tract secretions, nausea, vomiting)
	3	Discontinue inappropriate interventions (blood tests, antibiotics, intravenous fluids or drugs, turning regimens, vital signs)
	4	Document 'not for cardiopulmonary resuscitation'
Psychological and insight issues	5	Ability to communicate in English assessed as adequate (translator not needed)
	6	Insight into condition assessed
Religious and spiritual support	7	Religious and spiritual needs assessed with patient and family
Communication with family and others	8	Identify how family or other people involved are to be informed of patient's impending death
	9	Family or other people involved given relevant hospital information about access and contacts
Communication with primary health care team	10	General practitioner is aware of patient's condition
	11	Plan of care explained and discussed with patient and family
	12	Family or other people involved express understanding of plan of care.
Care after death	13	General practitioner informed
	14	Procedure for laying out explained
	15	Procedure following death discussed
	16	Family given information re procedures
	17	Policy about valuables in place
	18	Necessary documentation given to family
	19	Bereavement leaflet given

15.8.1 Resuscitation and advance directives

Individuals prepare for death by completing any 'unfinished business', for example, signing wills, contacting loved ones, appointing a power of attorney. Any advanced health directive should be honoured and issues surrounding resuscitation discussed. Early and ongoing advanced care planning is important and health practitioners should initiate end-of-life conversations and advanced care planning as early as appropriate. Patients' wishes regarding practical issues such as parenteral feeding, antibiotics and intravenous fluids should be explored. Each individual should also be given the opportunity to voice their wishes regarding desired place of death and who should be present at the time of death. These discussions can only follow frank and open discussions with patients and families about the current medical status and prognosis.

Occasionally patients and/or their relatives or carers will express a wish that the patient die or have their early death facilitated. Patients requesting euthanasia are often asking for an end of their suffering rather than for an end of their life. Such requests are often not repeated when distressing symptoms are addressed and controlled. Request for euthanasia has been linked to depression.[94]

Recommendation	Level	References
All patients requesting euthanasia should be thoroughly assessed in terms of their symptoms and mental wellbeing, and in particular, for evidence of depression. All symptoms should be managed, including offering treatment and counselling for depression if present.	III	94

Key point:

- Early and ongoing advanced care planning is important and health practitioners should initiate end-of-life conversations and advanced care planning as early as appropriate.

15.8.2 Symptom management in dying patients

The aim of palliative care in the terminal phase is to provide good symptom control for the patient, support for their carers, and to neither hasten death nor prolong the dying phase. As death approaches, nonessential medications should be discontinued and all medicines essential for the maintenance of symptom control continued and delivered by an appropriate route. While most drugs are delivered subcutaneously in a 24-hour infusion, the rectal, sublingual and transdermal routes provide an alternative option. Pain is the most common and most feared symptom of advanced disease and analgesics must always be continued. Adequate pain relief does not hasten death.[95] Similarly, antiemetics, corticosteroids, antipsychotics and sedatives may all be necessary for symptom relief.[96] Anticholinergics should be available in anticipation of the development of noisy breathing secondary to retained secretions in the large airways ('death rattle').Terminal restlessness is a state of agitation and unease often witnessed in dying patients. The reversible causes of this agitation (eg urinary retention, faecal impaction or pain) should be actively sought and treated. The cause is often unknown or unclear, and sedation is used as a means of symptom control. All opioids and sedatives are titrated carefully according to symptom response. Guidelines for symptom management in the dying patient are detailed in *Therapeutic guidelines: palliative care*.[35]

Recommendation	Level	References
Non-essential medications should be discontinued and essential medications should be prescribed by an appropriate route.	IV	96

Key point:

- Pain is the most common and most feared symptom of advanced disease and analgesics must always be continued.

15.8.3 Place of death

The majority of people in the general population and those with cancer would prefer to die at home.[97,98] Despite this, only a minority of patients die at home.[99] This reflects the changing needs of a patient during their illness trajectory. Some of the factors that make it more likely the patient is able to

die at home include involvement of a community palliative care service, perceived family support, and avoidance of hospitalisation.[100,101] It is important to determine whether the patient and family have a preferred place of death and to monitor this during their illness. If that preference is for dying at home, involvement of a community palliative care service can make this more likely to occur.[100,101]

Key point:

- Involvement of a community palliative care service makes it more likely that the patient will die at home.

15.9 Bereavement and support of families

Anticipatory grief is the process by which friends and family come to terms with the potential loss of a significant person. This may well be of particular relevance in patients with slowly progressive brain tumours. Patients and relatives can be supported through open discussion, clarification of likely outcomes and life review processes.[102]

Spiritual and religious support with an appropriate cultural focus should be offered both to the patient, and to the family after death in the context of bereavement support.[103]

As the patient enters the terminal phase, increasing distress is experienced as patients and families anticipate and prepare for death. An individualised approach to bereavement care is required as distress experienced by the patient and each family member is different in its nature, intensity and duration.[104]

On admission to palliative care, an assessment will assist the team in individualising pre-death support and bereavement care, helping long-term adjustment. Useful assessment criteria include age of patient and family, coping mechanisms, evidence of mental illness and cumulative multiple losses, perceived support and degree of family cohesion. Following death, other factors to consider include relationship and the nature of that relationship to the deceased, nature of death and whether the death was unexpected or perceived as traumatic.[105]

Common fears for people in the end stages of life include uncontrolled symptoms and 'being a burden'. Honest and appropriately paced communication will often assist in minimising these fears as death approaches. Support includes the provision of information that assists the patient and family in discussing treatment decisions and bodily changes. Additional skills such as aiding communication in families, opening conversations with children, acknowledging the patient's life contributions, exploring spiritual and religious dimensions, and preparing the funeral together, can also help to prepare for death. Discussion and completion of documents, such as power of attorney and advanced health directives, can provide guidance for treatment and an understanding of the desires of the patient and family.

Following death, most but not all grieving people experience numbness, intense distress, anxiety, yearning and loss of concentration. In addition, physical signs of stress, sleep and appetite disturbances can occur. Not all bereaved will require psychological interventions as protective factors such as positive coping patterns, an optimistic personality, social support and faith will assist in buffering against the stress of bereavement. However health professionals who are aware of the psychological reactions and possible social and cultural influences may assist the bereaved through normalising and providing psycho-education about the constantly changing responses. Assisting the bereaved in coping with the loss and in making adjustments to changes in life through encouraging them to share positive memories, establish goals and plan activities that provide pleasure can help to promote wellbeing. Complicated grief will occur for a small percentage of the bereaved, and further

studies are required to understand interventions that are helpful for this group. However, health professionals can help the bereaved to identify early warning signs and seek help. These signs may include persistent hopelessness, depression, suicidal ideation, continuing physical symptoms, lack of ability to function and misuse of drugs.[106–108] For family members who are dealing with challenging bereavement issues (such as complicated grief) various support systems are available including oncology or palliative care social workers, community nurses or psychologists who knew the patient. Alternatively, the family member may seek help from their own GP who may refer them on to a psychiatrist or psychologist if needed.

Key points:

Risk factors for complicated grief include:[105]

- Male gender
- Lack of coping mechanisms
- History of mental illness
- Multiple losses
- Intense brief relationship with deceased
- Lack of support and family cohesion
- Unexpected or traumatic death
- Financial difficulties

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APPENDIX 1 WORKING PARTY MEMBERSHIP AND CONTRIBUTORS TO GUIDELINES

Brain Tumour Guidelines Working Party

Professor Michael Barton OAM	Radiation Oncology, NSW (Chair)
Professor Bruce Barraclough AO	Medical Director, ACN *(until 31 December 2007)* NSW
Dr Michael Bynevelt	Radiology, WA
Associate Professor Frances Boyle AM	Medical Oncology, NSW
Dr Lawrence Cher	Neurology, VIC
Associate Professor Andrew Cole	Rehabilitation Medicine, NSW
Ms Laraine Cross	Social Work / Brain Tumour Australia, NSW
Dr Kate Drummond	Neurosurgery, VIC
Dr Ron Freilich	Neurology, VIC
Professor Janet Hardy	Palliative care, QLD
Dr Elizabeth Hovey	Medical Oncology, NSW (Project Officer)
Dr Margot Lehman	Radiation Oncology, QLD
Dr Anna Nowak	Medical Oncology, WA
Dr William Patterson	Medical Oncology, SA
Emeritus Professor Tom Reeve AC CBE	Senior Medical Advisor-ACN, NSW (Convenor)
Dr Michael Rodriguez	Neuropathology, NSW
Professor Mark Rosenthal	Medical Oncology, VIC
Dr Gail Ryan	Radiation Oncology, VIC
Dr Sally Smith	Public Health, NSW
Mr Denis Strangman	Consumer / International Brain Tumour Alliance, ACT
Dr Charles Teo	Neurosurgery, NSW
Associate Professor Jane Turner	Psychiatry, QLD
Dr David Walker	Neurosurgery, QLD
Dr Jonathan Wood	Neurology, NSW
Dr Helen Wheeler	Medical Oncology, NSW
Ms Christine Vuletich	ACN Secretariat
Ms Alice Winter-Irving	ACN Secretariat

Chapter leaders and their sub-committees

1. Setting the Scene

Dr Sally Smith*	Public Health, NSW
Professor Michael Barton OAM	Radiation Oncology, NSW

2. Approach to Patient

Dr Elizabeth Hovey*	Medical Oncology, NSW
Associate Professor Frances Boyle AM	Medical Oncology, NSW
Ms Laraine Cross	Social Work / Brain Tumour Australia, NSW
Dr Kate Drummond	Neurosurgery, VIC
Dr Michael Jefford	Medical Oncology, VIC
Ms Louise Sharpe	Psycho-oncology, NSW
Ms Rhea Stein	Psycho-oncology, NSW
Associate Professor Jane Turner	Psycho-oncology, QLD

3. Clinical Trials and Research

Dr Anna Nowak*	Medical Oncology, WA
Associate Professor Martin Stockler	Medical Oncology, and Public Health, NSW
Dr Nik Zeps	Basic Science and, Medical Ethics

4. Clinical Presentation

Dr Ron Freilich*	Neurology, VIC
Dr Marion Harris	Medical Oncologist, VIC
Dr Helene Roberts	Neurologist, VIC
Dr Anita Vinton	Neurologist, VIC

5. Imaging

Dr Michael Bynevelt*	Radiology, WA

6. Diagnosis and Pathology

Dr Michael Rodriguez*	Neuropathology, NSW
Associate Professor Michael Gonzales	Neuropathology, VIC

7. Low grade astrocytomas

Dr Charles Teo*	Neurosurgery, NSW
Dr Ross Jennens	Medical Oncology, VIC
Dr Gail Ryan	Radiation Oncology, VIC
Dr David Walker	Neurosurgery, QLD

8. High Grade Astrocytomas

Dr Kate Drummond*	Neurosurgery, VIC
Professor Michael Barton OAM	Radiation Oncology, NSW
Dr Guy Bryant	Radiation Oncology QLD
Dr Craig Carden	Medical Oncology, VIC
Dr Raymond Cook	Neurosurgery, NSW
Dr Michael Dally	Radiation Oncology, VIC
Dr Adam Fowler	Neurosurgery Trainee, NSW
Dr Margot Lehman	Radiation Oncology, QLD
Dr Jason Lickliter	Medical Oncology, VIC
Dr Bulent Omay	Neurosurgery, VIC (Turkey)
Professor Mark Rosenthal	Medical Oncology, VIC

9. Oligodendrogliomas

Dr Lawrence Cher*	Neurology, VIC
Dr Rosemary Harrup	Medical Oncology/Haematology, TAS
Dr Renate Kalnins	Anatomical Pathology, VIC
Dr Anna Nowak	Medical Oncology, WA
Dr Mandy Taylor	Radiation Oncology, WA

10. Complementary, alternative and unproven therapy

Dr William Patterson*	Medical Oncology, SA
Emeritus Professor Tom Reeve AC CBE	Senior Medical Advisor-ACN, NSW (Convenor)
Mr Denis Strangman	Consumer / International Brain Tumour Alliance, ACT

11. Symptom management and complications

Dr Jonathan Wood*	Neurology, NSW
Dr Neil Anderson	Neurology, Auckland New Zealand
Dr Rob Lindeman	Haematology, NSW
Associate Professor Ernest Somerville	Neurology, NSW
Dr John Sullivan	Dermatology, NSW
Dr Oril Wargon	Dermatology, NSW

12. Psychosocial care

Associate Professor Jane Turner*	Psychiatry, QLD
Ms Georgina Haysom	Senior Solicitor, Avant Insurance Limited
Dr Stephen Lee	Neuropsychology, NSW

13. Rehabilitation

Associate Professor Andrew Cole*	Rehabilitation Medicine, NSW
Dr Greg Bowring	Rehabilitation Medicine, NSW
Dr David Eckerman	Rehabilitation Medicine, QLD
Professor Janet Hardy	Palliative care, QLD
Dr Neil Johns	Rehabilitation Medicine, VIC
Dr Kathy McCarthy	Rehabilitation Medicine, NSW
Ms Ornissa Naidoo	Occupational Therapy, QLD

14. Follow-up

Dr Margot Lehman*	Radiation Oncology, QLD
Dr Stephen Stuckey	Radiation Oncology, VIC

15. Palliative care

Professor Janet Hardy*	Palliative Care, QLD
Dr Mark Deuble	Palliative Care, QLD
Dr Phillip Good	Palliative Care, NSW
Ms Ornissa Naidoo	Occupational Therapy, QLD
Ms Gabrielle O'Connor	Nursing, Palliative Care/Neuro-oncology, VIC
Associate Professor Rohan Vora	Palliative Medicine, QLD
Ms Julie Walters	Liaison Librarian, QLD

Glossary

Emeritus Professor Tom Reeve AC CBE*	Senior Medical Advisor, ACN / Convenor, Working Party, NSW
Professor Michael Barton OAM	Radiation Oncology, NSW
Dr Elizabeth Hovey	Medical Oncology, NSW

* Chapter leader

Review Process:

Internal Reviewers

Professor Michael Barton OAM	Radiation Oncology, NSW
Dr Elizabeth Hovey	Medical Oncology, NSW
Dr Anna Nowak	Medical Oncology, WA
Dr Sally Smith	Public Health, NSW
Mr Denis Strangman	Consumer, ACT

Invited External Reviewers

Dr Meera Agar
Dr Helen Austin
Professor Susan Chang
Dr Di Clifton
Professor Noel Dan
Professor Robert DePompolo
Associate Professor Michael Fearnside AM
Professor Graham Giles
Associate Professor Afaf Girgis
Professor Paul Glare
Dr Eng-Siew Koh
Mr Denis Strangman
Mr Ross Symons
Dr Mo Mo Tin

External Expert Review Panel

Professor Michael Frommer (Chair)	
Associate Professor Frances Boyle AM	
Dr Michael Buckland	
Ms Kaye Duffy OAM	
Dr Monika Janda	
Dr Elizabeth Hovey	Project Officer, BTGLWP*
Ms Sally Payne	
Emeritus Professor Tom Reeve AC CBE	Convenor, BTGLWP*
Associate Professor Daniel Roos	
Associate Professor Jeffrey Rosenfeld	
Dr Brindha Shivalingam	

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APPENDIX 2 – GLOSSARY AND ABBREVIATIONS

Glossary

Activated partial thromboplastin time (APTT)	APTT measures the time necessary to generate fibrin from initiation of the intrinsic pathway.
Astrocytoma	A tumour of central nervous system composed of astrocytes.
Cognitive	Mind function and awareness, perception, thinking and memory.
D- dimer	A test to detect the production of fibrin breakdown products following conversion of fibrinogen to fibrin. This is frequently elevated in the setting of thromboembolism.
Fluorescence in situ hybridization (FISH)	This is a pathology test that measures the amount of a certain gene in cells.
Glioblastoma multiforme (GBM)	The most malignant type of glioma. Grade IV on WHO classification of gliomas.
Glioma	A tumour of neuroglia at any stage of development.
Gray	The gray (symbol: Gy) is the SI unit of absorbed radiation dose. One gray is the absorption of one joule of radiation energy by one kilogram of matter.
Hemiparesis	Partial paralysis or muscular weakness involving half of the body.
Hemiplegia	Paralysis of one side of the body.
IVC filter	A filtration device inserted in the inferior vena cava to prevent pulmonary emboli.
Karnofsky performance status.	A performance measure for rating the ability of a person to perform usual activities, evaluating a patient's progress after a therapeutic procedure, and determining a patient's suitability for therapy. It is used most commonly in the prognosis of cancer therapy, usually after chemotherapy and customarily administered before and after therapy.
Li Fraumeni Syndrome	A rare autosomal dominant hereditary disorder. Li-Fraumeni syndrome increases greatly the susceptibility to cancer. The syndrome is due to a mutation in the p53 tumor suppressor gene, which normally helps control cell growth.
Magnetic Resonance Spectroscopy	Magnetic resonance spectroscopy (MRS) is different from MRI because MRS uses a continuous band of radio wave frequencies to excite hydrogen atoms in a variety of chemical compounds other than water. These compounds absorb and emit radio energy at characteristic frequencies, or spectra that can be used to identify them.
Oligodendroglioma	A tumour of oligodendrocytes. Majority in white matter of the brain. Can be low grade (grade II) or high grade (usually grade III)
PCV	Procarbazine plus lomustine (CCNU) plus vincristine. This is a combination of three types of chemotherapy that has been administered predominantly in the scenario of oligodendroglioma (though also in the setting of astrocytoma in the past).
Technetium	^{99m}Tc diethylenetriamine pentaacetate. A radionuclide chelate complex used for nuclear medicine imaging and function testing; also known as 99mTc pentatate [diethylene triamine pentaacetic acid].
Wiki	A website that uses wiki software, allowing the easy creation and editing of any number of interlinked Web pages within the browser. Wikis are often used to create collaborative websites, to power community websites, and for note taking.

Abbreviations

^{18}FFDG	^{18}F-Fluorodeoxyglucose
^{201}Ti	Thallium
99m TcDTPA	Technetium ^{99m}Tc diethylenetriamine pentaacetate
ADC	Apparent diffusion coefficient
AED	Anti-epileptic drug
AF	Accelerated fraction
AGPS	Australian Government Printing Services
AIHW	Australian Institute of Health and Welfare
APTT	Activated partial thromboplastin time.
AUC	Area under the curve
AYLL	Average person years of life lost
BCNU	bischloroethylnitrosourea (Carmustine)
CAM	Complementary and alternative therapy
CBV	Cerebral blood volume
CBZ	Carbamezepine
CCNU	cyclohexylchloroethylnitrosourea (Lomustine)
CI	Confidence Interval
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computerised Tomography (imaging device)
CTV	Clinical target volume
DNA	Deoxyribonucleic acid
DTI	Diffusor tensor imaging
DTIC	Dacarbazine (chemotherapy)
DVT	Deep venous thrombosis
DYF Quick	A cytological stain
ECOG	Eastern Cooperative Oncology Group
EIAED	Enzyme-inducing anti-epileptic drug
FISH	Fluorescence in situ hybridization.
FLAIR	Fluid attenuated inversion recovery (MRI)
GBM	Glioblastoma multiforme
GBP	Gabapentin, an antiepileptic drug
GTV	Gross tumour volume
GuMRI	Gadolinium enhanced magnetic resonance imaging
Gy	Gray

HF	Hyperfractionation
HGG	High grade glioma
HIT	Heparin induced thrombocytopaenia
HITT	Heparin-induced thrombocytopenia and thrombosis
HNPCC	Hereditary non-polyposis colon cancer
HR	Hazard Ratio
ICU	Intensive care unit
IFRT	Involved field radiotherapy
iMRI	Intraoperative MRI
IPC	Intermittent pneumatic compression
IQ	Intelligence quotient
IV	Intravenous
IVC	Inferior vena cava
KPS	Karnofsky performance status.
LEV	Leviteracitam, an anti-epileptic drug
LFS	Li Fraumeni Syndrome
LGA	Low grade astrocytoma
LGG	Low grade glioma
LMWHs	Low molecular weight heparins
LOH	Loss of heterozygosity. (Referring to chromosomal alterations or segmental losses)
LTG	Lamotrigine; a newer generation anti-epileptic drug
MDC	Multidisciplinary care
Methyl CCNU	methylcyclohexylchloroethylnitrosourea (semustine)
MGMT	O6-methylguanine-DNA methyltransferase
MRC	United Kingdom Medical Research Council
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NCCTG	North Central Cancer Treatment Group
NHMRC	National Health and Medical Research Council
NSAID	Non-steroidal anti-inflammatory drug
OA	Oligoastrocytoma
OG	Oligodendroglioma
ORR	Overall Response Rate
OS	Overall Survival
OXC	Oxcarbazepine, an antiepileptic drug

PAP	Perioxidase anti-perioxidase cytological stain
PBS	Pharmaceutical Benefits Scheme
PCV	Procarbazine plus lomustine (CCNU) plus vincristine.
PE	Pulmonary embolism
PET	Positron Emission Tomography.
PFS	Progression Free Survival
PHT	Phenytoin, an anti-epileptic drug
PRG	Pregabalin, an anti-epileptic (or anticonvulsant) drug
QOL	Quality of life
RBI	Radio-labelled compound- eg 3□-(4-iodophenyl)-2□-(tricarbonylrheniumcyclopentadienylcarboxym ethyl)tropane (RBI-211)
rCBV	Relative Cerebral Blood Volume (alternately Regional Cerebral Blood Volume)
RCT	Randomised Clinical Trial
RPA	Recursive partitioning analysis
RTOG	Radiation Therapy Oncology Group. This is an international cooperative trial group participating in trials assessing radiation therapy in different settings.
SES	Socioeconomic status
SPECT	Single Photon Emission Computed Tomography
T_1	Signal characteristics of magnetic resonance
T_2	Signal characteristics of magnetic resonance
TD	Tolerance dose of radiation (defined as 5% complication rate in five years (TD5/5))
TGB	Tiagibine, an anti-epileptic drug
TTP	Time to progression
TPM	Topiramate, an anti-epileptic drug
UFH	Unfractionated Heparin
V/Q	Ventilation-Perfusion scan.
VEGF	Vascular endothelial growth factor
VPA	Valproic acid, also known as sodium valproate
VTE	Venous thromboembolism
WBRT	Whole brain radiotherapy

APPENDIX 3 GUIDELINES DEVELOPMENT PROCESS

Clinical Practice Guidelines for the Management of Adult Gliomas, Astrocytomas and Oligodendroglioma

Purpose, scope and development process of the Guidelines:

These Guidelines have been developed to provide information on malignant adult brain tumours (specifically gliomas) to medical practitioners and interested community members.

The aim is to improve the level of practice and understanding in a health area that causes considerable community anxiety.

Brain tumours also contribute heavily through costs of hospital, home and community management to the budget of the Australian health care system. They impose the highest economic burden on carers of any cancer, as well as significant emotional and physical challenges.

Methods of development for Clinical Practice Guidelines for the Management of Adult Gliomas, Astrocytomas and Oligodendroglioma:

The development of these clinical practice guidelines was commenced after a number of consultations between a wide range of professionals and community personnel who were under considerable community pressure to address what was considered to be a significant community burden. It had also been noted from patterns of care surveys (and a formal Victorian study[1]) that there were significant variations in practice around Australia in terms of what was being offered to glioma patients. Interested clinicians were keen to offer patients around Australia a uniform evidence-based approach to their management.

This activity was underway but progressing slowly when a generous donation was made to ACN to promote development of guidelines for managing malignant brain tumours in memory of the donor's wife who died from a glioma. The donor requested that a consumer version be developed to accompany the Guidelines. The patient had a difficult clinical course and had remarked during her illness that she wished there was a book outlining what standard practice was, as it was so difficult to know what was best to do at various points in her clinical course.

This same message was frequently reiterated and it was decided to develop a Working Party that would address the problem and keep an eye on assuring that advice would be given to help people over serious hurdles.

The first meeting of those interested parties present was rather diffident because of the costs incurred in developing guidelines to the rigorous requirements as outlined in "A Guide to Development, Implementation and Evaluation of Clinical Practice Guidelines. NHMRC, Canberra 1999." The cost of producing guidelines to this standard were seen to be an expensive matter when the initial group to promote the development process met in Sydney in March 2005 at the National Glioma Meeting. Further discussions took place at the COSA Annual Scientific Meeting in Brisbane in 2005 and decided to proceed without the imprimatur of the NHMRC.

A multidisciplinary representational Working Party was developed with the assistance of the ACN Secretariat. It was further decided to request the Cancer Council Australia (TCCA) and the Clinical Oncological Society of Australia (COSA) to undertake accreditation of the Guidelines, once developed, as it was not appropriate to seek NHMRC endorsement.

Working party progress

The first meeting of the defined Working Party took place in Sydney on 10 February 2006.

There was again careful consideration addressing finance and urgency before the consensus approach was chosen.

It was also planned to develop a desktop aide for GPs and a pamphlet for community interest.

A work plan was decided upon to develop Guidelines that would:

- Assist medical practitioners in their decision making in relation to managing malignant adult brain tumours.
- To promote better clinical assessment of malignant adult brain tumours.
- To provide increased understanding through education of medical carers and the community of all involved in the care of malignant adult brain tumours.

The Working Party planned to focus on outcomes, through assessing the best available scientific evidence and this became its activity until completion.

At its initial meeting, topics were decided and chapter leaders chosen. Chapter leaders were charged to develop teams of contributors to help them progress their chapter.

At a meeting on 22 September 2006, synopses of chapters were presented and showed good progress.

The Working Party Executive met in 2007 to review progress and a decision was taken to have chapter drafts ready for a review process by 25 December 2007.

Individual chapter reviews were undertaken before a public review process which took place in July 2008.

Following this review, an external review panel met in September 2008 and examined submissions and made recommendations for the final draft document.

The Executive of the Working Party edited the document in line with the independent reviewers' recommendations before sending it to TCCA and COSA for approval.

Designation of levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

In this document all level III has been listed as III regardless of category.

IV Evidence obtained from case series, either post-test or pre-test and post-test.
These levels of evidence ratings have been adapted from US Preventative Service Task Force (1989), *Guide to clinical preventative services: an assessment of the effectiveness of 169 interventions* (ed M Fisher), Williams and Williams, Baltimore, Appendix A, p388.

The process of developing the Guidelines was informed by *A guide to the development, implementation and evaluation of clinical practice guidelines*, NHMRC Canberra 1999.

Implementation

The level of implementation will depend on budget. It is aimed to have an electronic version posted for free access on the ACN website, as well as hard copies for those who request it. A Wiki will be developed to publish and update the guidelines.

It is planned that there will be educational launch activities throughout Australia with major input from chapter leaders and contributors from around Australia into these launch events. Various professional and community organisations will be asked to help in this activity.

It is also hoped that the specific recommendations of synoptic reporting for MRIs of brain tumours and pathology reporting will be taken up by radiologists and pathologists respectively throughout Australia. There many need to be specific launch activities for these groups.

We aim to encourage the Association of Neurosurgeons to distribute these guidelines to all their trainees as part of their mandatory training curriculum. Other associated organisations will be canvassed to assist prior to the final draft.

The newly formed national cooperative trials group for neuro-oncology (known as COGNO) will specifically be examining the guidelines in terms of where there are gaps in the guidelines and will aim to develop clinical trial protocols (or to participate in relevant international studies) where appropriate to address the gaps in our knowledge.

Maintenance

It is envisaged that the guidelines or parts thereof, will be updated where applicable electronically at regular intervals (eg two-three yearly) only in the areas where there is new high level evidence. We will retain a Working Party to facilitate these updates and monitor the content of the Wiki.

[i] Rosenthal MA, Drummond KJ, Dally M, Murphy M, Cher L, Ashley D, et al. Management of glioma in Victoria (1998-2000): retrospective cohort study. Med J Aust. 2006 Mar 20; 184(6):270-3.

Index to *Clinical practice guidelines for the management of adult gliomas: astrocytomas and oligodendrogliomas*