The treatment of malignant cerebral tumours

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Malignant cerebral tumours are uncommon. While a large proportion are resistant to conventional therapies there are a significant number of curable malignant brain tumours that require recognition and appropriate therapy.

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Compared to adult tumours such as lung and breast cancer, primary malignant cerebral tumours are uncommon, accounting for only 2–5% of all malignancies. The age-adjusted incidence is 6–12/100 000 and has shown no significant increase over the past 20 years. However, malignant brain tumours are second only to stroke as a cause of death from neurological disorders.

EPIDEMIOLOGY AND AETIOLOGY

Malignant cerebral tumours affect a predominantly ageing population, with a peak age at presentation of 65–75 years. However, primary brain tumours are also the second commonest malignancy in childhood and there is a second small peak in incidence at ages 0–14 years (Legler et al, 1999).

Little is known about the aetiology of most brain tumours. Radiation exposure in childhood is one of the few recognized risk factors and only a small minority are associated with dysgenetic syndromes such as neurofibromatosis. These are listed in *Table 1*.

CLASSIFICATION

Primary cerebral tumours are classified based on cell morphology and grade. The World Health Organization (WHO) classification system groups tumours by their cell of origin and grades them into grades I–IV based on measures of mitotic rate, necrosis and nuclear pleomorphism (Kleihues and Cavenee, 2000). The commonest malignant tumours classified in the WHO system are shown in *Table 2*. The term glioma is used to cover all tumours of neuroglial origin (*Table 2*), of which astrocytic tumours are the commonest. Of these, 40–50% are grade IV tumours (*Figure 1*), 30–40% grade III tumours and only 15–20% are well differentiated, low-grade tumours (*Figure 2*). Oligodendrogliomas and ependymomas account for less than 5% of adult tumours. Non-neuroepithelial tumours such as primary cerebral lymphomas and germ cell tumours account for less than 1% of adult brain tumours. In childhood the most common brain tumours are medulloblastoma, pilocytic astrocytoma, ependymoma and craniopharyngioma.

TABLE 1.
Dysgenetic syndromes with increased incidence of primary cerebral tumours

Syndrome	Tumour
Neurofibromatosis type 1	Optic nerve glioma, glioma, meningioma
Neurofibromatosis type 2	Acoustic neuroma, meningioma
Tuberous sclerosis	Giant cell astrocytoma
Von Hippel–Lindau disease	Haemangioblastoma
Li–Fraumeni syndrome	Astrocytoma

PROGNOSIS

The prognosis of malignant cerebral tumours is closely related to age and performance status as well as to histological and grade type. Median survival figures for the common tumour types are shown in *Table 3*. Low-grade gliomas (*Figure 2*) may progress slowly over many years with minimal symptoms and treatment is therefore indicated for progressive symptoms or if there is evidence of high-grade transformation. High-grade gliomas (*Figure 1*) are often symptomatic at presentation and carry a poor prognosis despite combined modality treatment.

TREATMENT

Surgery

The aims of surgery in primary cerebral tumours are to obtain tissue for histological diagnosis, to

achieve cytoreduction and to alleviate symptoms caused by mass effect. Histological diagnosis can be achieved at the time of tumour resection or as a separate biopsy procedure. Biopsy is most often carried out stereotactically, using a frame or frameless device to provide three-dimensional landmarks that locate the tumour precisely in three dimensions after cross-referencing with computed tomography (CT) or magnetic resonance imaging (MRI) data. Stereotactic biopsy can be carried out under intravenous sedation with local anaesthesia or under general anaesthesia.

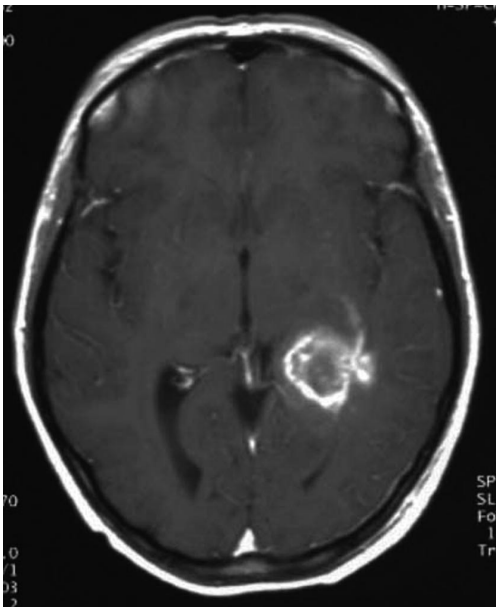

Figure 1. Enhanced T1-weighted magnetic resonance image of mixed density lesion, which on biopsy was shown to be a grade 4 astrocytoma.

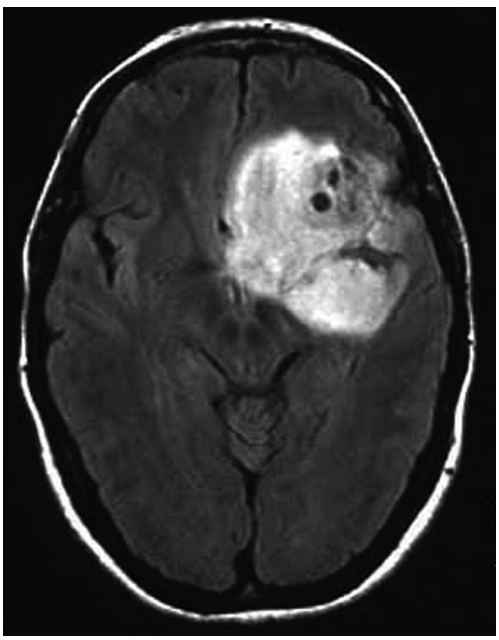

Figure 2. Magnetic resonance image (FLAIR sequence) of an unenhancing low density lesion on T1-weighted images (not shown) suggestive of a low grade glioma (grade 2 astrocytoma or oligodendroglioma).

The morbidity from stereotactic biopsy is low: 3.3% minor (e.g. fits, superficial infection) and 1.3% major (haemorrhage, cerebral infection or new neurological deficit) and the diagnostic yield is greater than 90% (Kondziolka and Lunsford, 1999). Few cerebral lesions are treated

TABLE 2.
Common subtypes of malignant neuroepithelial cerebral tumours (World Health Organization classification)

Tumour		WHO malignancy grade
Astrocytic tumours	Diffuse astrocytoma	II
	Fibrillary	II
	Protoplasmic	II
	Gemistocytic	II
	Anaplastic astrocytoma	III
	Glioblastoma	IV
	Giant cell glioblastoma	IV
	Gliosarcoma	IV
	Pilocytic astrocytoma	I
	Pleomorphic xanthoastrocytoma	I–III
	Subependymal giant cell astrocytoma (tuberous sclerosis)	I
Oligodendroglial tumours	Oligodendroglioma	II
	Anaplastic oligodendroglioma	III
Mixed gliomas	Oligo-astrocytoma	II
	Anaplastic oligo-astrocytoma	III
Ependymal tumours	Ependymoma	II
	Cellular	II
	Papillary	II
	Clear cell	II
	Tanycytic	III
	Myxopapillary ependymoma	I
	Subependymoma	I

From Kleihues and Cavenee (2000)

TABLE 3.
Median survival of patients with cerebral tumours

Tumour type		Median survival	5-year survival
Astrocytic tumours	Astrocytoma grade II	5–12 years	50–70%
	Astrocytoma grade III	18–30 months	<10%
	Astrocytoma grade IV	9–12 months	<2%
Oligodendroglial tumours	Well-differentiated	4–10 years	30–50%
	Anaplastic	3–5 years	20–40%
Primary cerebral lymphoma		12–24 months	30–40%
Medulloblastoma		5–10 years	50–70%

without a histological diagnosis. The exceptions are lesions such as brainstem glioma with typical radiological features, when the risks of biopsy outweigh the likely benefit, cranial germ cell tumours with diagnostic elevation of serum markers and elderly disabled patients with typical features of malignant glioma when the management intent is palliative.

The role of resection as primary treatment depends on the tumour site and histology as well as the patient's general and neurological status. Extensive resections of brain tumours are associated with <1% mortality and low morbidity (Vives and Piepmeier, 1999), and the expected hospital stay after uncomplicated craniotomy is less than 7 days. Advances in surgical technique including intraoperative imaging, functional MRI and the use of navigational devices, which link imaging data with surgical anatomy, and help in optimizing craniotomy access, defining the best surgical approach and reducing morbidity.

Even with optimal surgery, removal of all malignant tissue is not possible because of diffuse infiltration of surrounding normal brain by tumour cells. Although extensive resection will reduce tumour bulk and improve symptoms of mass effect there is no direct evidence that more extensive surgery improves survival in the most common tumour types. In high-grade gliomas, studies have shown prolonged survival in patients who underwent maximal resection although other studies do not confirm it. These data are open to selection bias as surgery is more frequently carried out in fitter, younger patients with a better prognosis and this issue has never been addressed in a randomized trial (Hess, 1999).

The role of surgery in low-grade astrocytic tumours is also controversial. Surgery in patients with low-grade gliomas is favoured if tumour removal is likely to improve symptoms, for example in patients with large lesions causing mass effect (Bampoe and Bernstein, 1999). Radical resection is carried out in patients with apparently localized tumours as an experimental procedure but the long-term benefit of this approach has not been defined. In patients with high- and low-grade gliomas in or close to eloquent areas of the brain with a risk of neurological deterioration surgery is inappropriate.

Initial radical surgery is an important part of radical treatment in pilocytic astrocytomas, where complete excision may be curative, and medulloblastomas where radical surgical removal combined with radiotherapy give the best chance of long-term disease control and survival. Patients with suspected cranial germinomas (*Figure 3*), usually presenting in pineal or suprasellar regions, and patients with periventricular enhancing masses suggestive of CNS lymphoma should have biopsy alone without attempt at surgical resection.

Radiotherapy

Conventional radiotherapy: Conventional external beam radiation is an established therapeutic modality for patients with incompletely resected malignant CNS tumours. Radiation is delivered using a high-energy photon beam from a linear accelerator or cobalt-60 unit. The tumour volume is defined on CT or MRI and the target area to be irradiated includes visible tumour and rim of 2–3 cm to include likely microscopic disease. Patients are immobilized for treatment, usually in an individually made plastic shell, and treatment is carried out 5 days a week for 5–6 weeks to give a radiation dose of 55–60 Gy.

In high-grade gliomas postoperative radiotherapy was shown in randomized studies to improve median survival by 5–6 months (to a median survival of 9–12 months) and may improve performance status in up to one-third of patients (Walker et al, 1979; Kristiansen et al, 1981). However, long-term tumour control is rarely achieved. In elderly patients with poor performance status who represent the poorest prognosis group, 6 weeks radiotherapy may not be appropriate. Supportive care alone or a shortened palliative course of radiotherapy may be more acceptable (Thomas et al, 1994; Brada et al, 1995; Kleinberg et al, 1997).

In low-grade astrocytic tumours there is no evidence that radiotherapy early in the course of

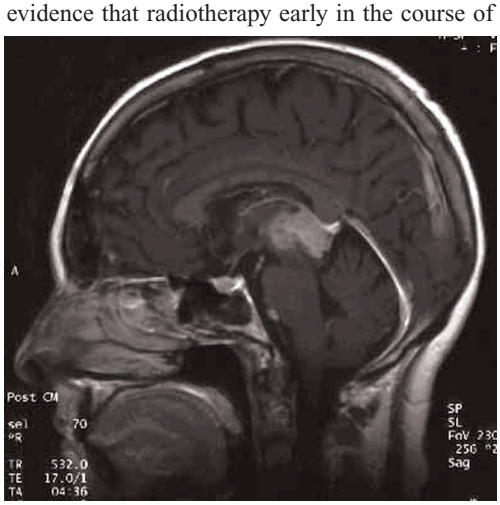

Figure 3. Enhanced sagittal T1-weighted magnetic resonance image showing a pineal region tumour. The differential diagnosis lies between cranial germ cell tumour (germinoma or nongerminomatous cranial germ cell tumour), primary pineal tumour (pineocytoma or pineoblastoma), glioma or other less common tumours.

disease improves outcome (Karim et al, 1998). It is therefore reserved for symptomatic patients with progressive disease. Conventional treatment is similar to radiotherapy in high-grade tumours.

Radiotherapy alone is curative treatment for cranial germinoma and is an effective adjuvant in cranial non-germinomatous germ cell tumours following chemotherapy.

Localized radiotherapy to the area of brain where there is known tumour or high risk of recurrence is also part of standard postoperative treatment of ependymoma and is part of primary management of cerebral lymphomas in conjunction with chemotherapy. In medulloblastoma, with a high propensity to seed through the CSF, irradiation of the whole brain and spinal cord is indicated as part of curative therapy.

New radiotherapy techniques

Stereotactic irradiation: Evidence that glioma cells survive at the site of the primary tumour after conventional radical radiotherapy has prompted the introduction of methods to increase the radiation dose to the tumour while sparing normal brain. These rely on accurate localization of the tumour in three dimensions and localized irradiation. This can be given either accurately focussed external beam irradiation (stereotactic radiotherapy/radiosurgery) or implantable radioactive sources (interstitial radiotherapy), which is an invasive technique currently rarely used. Stereotactic radiotherapy/radiosurgery uses multiple, small beams from a linear accelerator or from a multi-headed Co-60 unit (described as a gamma knife) focussed onto the tumour.

Both techniques have been used to increase the dose to small malignant tumours following conventional radiotherapy. However, such high doses of radiation carry a significant risk of brain necrosis requiring reoperation and tumours continue to recur locally (Sneed et al, 1994). The only published randomized trial of interstitial radiotherapy has not demonstrated survival benefit in patients with malignant glioma (Laperriere et al, 1998) and randomized studies of radiosurgery and fractionated stereotactic radiotherapy are underway. Currently, the only indication for radiosurgery (stereotactic radiotherapy) in malignant tumours is in the treatment of solitary brain metastases.

Boron neutron capture therapy: Boron neutron capture therapy (BNCT) is an experimental technique of irradiation that is designed to produce selective tumour irradiation through locally generated radioactive species. This relies on capture of low energy (thermal) neutron particles by ^{10}B (boron) which releases a particles and ^{7}Li (lithium) ions. These produce dense local ionizations with a range of 5–9 μm.

To achieve selective local irradiation a high ^{10}B concentration must be present in the tumour and a lower concentration in normal brain and blood. Experimental BNCT is carried out using infusion of ^{10}B-borophenylalanine (BPA) or borosulphydryl (BSH) which localize in tumours, followed by thermal neutron irradiation from an external source, produced by a nuclear reactor or an accelerator. This technique is currently in phase I/II trials in patients with gliomas (Buchholz et al, 1997).

Chemotherapy

Malignant gliomas are among the more chemoresistant of solid tumours although some subgroups, such as anaplastic oligodendrogliomas, are highly chemoresponsive (Cairncross, 1994). The value of chemotherapy as part of initial management after surgery and radiation in high-grade gliomas remains controversial. It is likely that only a small sub-group of patients benefit from adjuvant chemotherapy, and the overall magnitude of survival benefit

TABLE 4.
Chemotherapy used in patients with glial tumours

Drug	Standard dose/route	Toxicity
BCNU (carmustine)	200–240mg/m^2 intravenously 6–8 weekly	Leukopenia, thrombocytopenia, nausea and vomiting, pulmonary fibrosis
CCNU (lomustine)	100–130mg/m^2 by mouth 6–8 weekly	Leukopenia, thrombocytopenia, nausea and vomiting
Procarbazine	150mg/m^2 by mouth daily x14 days 4-weekly	Leukopenia, thrombocytopenia, nausea and vomiting, rash, encephalopathy
Vincristine	1.4mg/m^2 intravenously 4 weekly	Peripheral neuropathy, autonomic dysfunction
PCV regimen (MRC, UK) Repeated 6-weekly	CCNU 100 mg/m^2 day 1 vincristine 1.5mg/m^2 day 1, procarbazine100 mg/m^2 days 1–10	As above
PCV regimen (USA) Repeated 6-weekly	CCNU 110 mg/m^2 day 1, vincristine 1.4mg/m^2 days 1 and 29, procarbazine 60mg/m^2, days 8–21	As above
Temozolomide	200mg/m^2 orally daily, 5 days, 4 weekly	Thrombocytopenia

BCNU = carmustine; CCNU = lomustine

from meta-analyses (Fine et al, 1993) and large randomized trials (Brada et al, 1998b) is smaller without increase in cure rate. The most commonly used chemotherapy regimens in glioma patients are shown in *Table 4*.

Adjuvant chemotherapy is not standard practise in the UK and chemotherapy is usually reserved for recurrent disease after surgery and radiotherapy. Response rate to nitrosourea-containing chemotherapy (BCNU or PCV) in recurrent high-grade gliomas is in the region of 10–40%. Trials of agents such as cisplatin and paclitaxel have not to date been shown to improve response rate or survival. Newer drugs including temozolomide have shown promising response rates in anaplastic astrocytomas but have yet to be compared to standard nitrosourea-containing regimen (Batchelor, 2000; Yung, 2000).

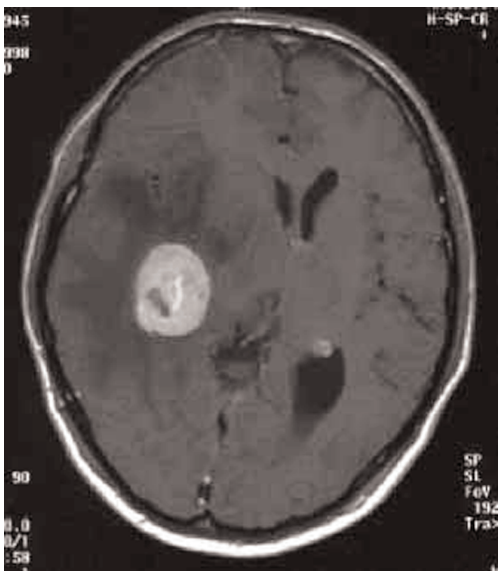

Figure 4. Enhanced T1-weighted magnetic resonance image of a periventricular lesion, which on biopsy was shown to be a B cell lymphoma (primary central nervous system lymphoma).

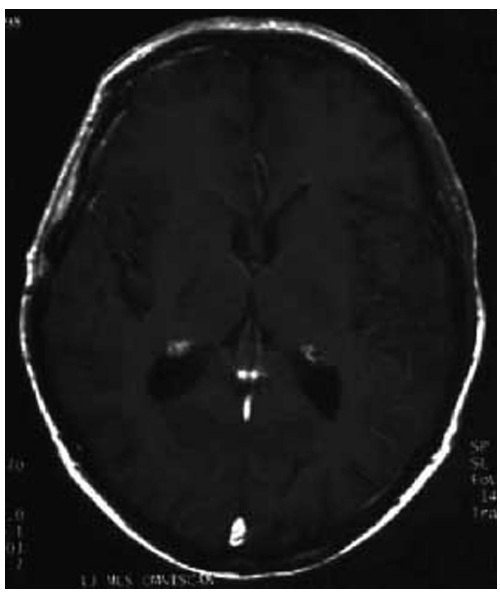

Figure 5. Primary central nervous system lymphoma following therapy (patient as in Figure 4*).*

Primary chemotherapy including high dose methotrexate is part of the standard management of primary cerebral lymphomas (*Figures 4* and *5*) this is currently followed by radiotherapy (Brada et al, 1998a; DeAngelis, 1999; Nasir and DeAngelis, 2000). Chemotherapy is also used in the treatment of childhood brain tumours particularly in children under 4 years of age. Chemotherapy is also a component of curative therapy in cranial non-germinomatous germ cell tumours and medulloblastomas.

Experimental therapeutic approaches

Gene therapy: Gliomas are obvious targets for gene therapy, as they remain localized within a single organ and because of poor efficacy of conventional treatment. Gene therapy strategies are aimed at modifying the genotype of tumour cells to alter the malignant phenotype or promote cell death. Potential targets for gene therapy are changes in tumour suppressor genes, cell-cycle modulators and growth factors that occur during malignant tumour progression. All gene therapy techniques require an efficient and safe method of gene transfer in vivo and this has so far been a major obstacle to success in this field. The most promising method uses adenoviral vectors to transport genetic material into the host cells, but the ideal vector, which is safe and can be administered systemically, has yet to be developed.

An alternative gene therapy strategy, which does not target a specific molecular abnormality, is the 'suicide gene' method. In this approach, a viral vector is used which carries a gene coding for an enzyme that modifies a non-toxic prodrug. When the drug is delivered systemically, only tumour cells that have taken up the new genetic material and have the prodrug conversion enzyme are killed. Clinical trials have been carried out using herpes simplex virus thymidine kinase gene carried in a viral vector. This is injected directly into the tumour site and confers sensitivity to ganciclovir, which is phosphorylated and converted to a cytotoxic agent that blocks DNA replication (reviewed by Alemany et al, 1999). Other prodrug enzyme combinations are currently under test.

Other experimental strategies: Alternative approaches that do not rely on killing tumour cells directly are being investigated. These include agents which target the tumours' blood supply, such as thalidomide which inhibits new vessel

formation (Fine et al, 2000), or target tumour cell invasion through the matrix metalloproteinase inhibitor Marimastat. Inhibitors of specific growth-factor signalling pathways known to be upregulated in gliomas are also being developed, for example SU-101 (leflunomide) which is a specific inhibitor of the platelet-derived growth factor (PDGF) pathway. Results of phase I/II trials of these agents in glioma patients are awaited.

Medical management

In addition to specific treatments directed at tumour eradication or control, all patients with gliomas should receive appropriate medical and supportive care. Many patients present with features of raised intracranial pressure and a short course of corticosteroids, such as dexamethasone 4–16 mg daily, is often indicated to alleviate symptoms. The dose should be reduced as soon as possible to prevent long-term side-effects such as proximal myopathy that can add significantly to disability. Long-term anticonvulsant treatment is recommended in patients presenting with epilepsy. There is no evidence to support its use in preventing epilepsy following neurosurgical intervention in patients without a previous history of fits.

In patients with poor prognosis tumours and poor performance status supportive care alone may be the most appropriate management strategy. The distress associated with the knowledge of the diagnosis and prognosis is a cause of significant morbidity. Psychological as well as practical support is an important part of management both in hospital and in the community. **HM**

Conflict of interest: none.

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KEY POINTS

- Primary cerebral tumours account for only 2–5% of malignancies, a small proportion of these occur as part of dysgenetic syndromes.
- Malignant brain tumours are not curable by surgery alone. Radical resection is a component of therapy of medulloblastoma and ependymoma.
- The role of radical surgery remains unproven in high grade and low grade gliomas.
- External beam radiotherapy is the primary therapy in malignant glioma and cranial germinoma and adjuvant therapy in medulloblastoma .
- Chemotherapy is a component of treatment of primary cerebral Lymphoma, non-germinomatous germ cell tumours and medulloblastoma.
- New radiotherapy techniques including stereotactic irradiation/radiosurgery are being assessed as additional treatment of small malignant gliomas but have little role in the treatment of malignant brain tumours other than solitary brain metastases.
- Experimental treatment approaches in malignant gliomas include gene therapy and agents that target tumour blood vessels.