Management of primary malignant brain tumours

Anaplastic astrocytoma and glioblastoma multiforme comprise the largest proportion of malignant supratentorial glioma. Most clinical and research papers considering aspects of either malignant glioma biology or treatment, contain, within the opening paragraph, a conditional statement similar to that first used by Bailey and Cushing in their 1926 monograph on brain tumours. The statement usually reads “despite recent advances in neuroimaging, microneurosurgery, radiotherapy, and chemotherapy malignant gliomas remain incurable”. This group of neoplasms of the nervous system is the third commonest cause of cancer related death in young and middle aged adults. Perhaps even more depressing is that despite advances in investigative and therapeutic technology, a plethora of novel therapeutic approaches, and an increasing knowledge about their biology there has also been no major advance in the life expectancy of patients afflicted with these neoplasms. Despite the highly variable quality of an increasingly voluminous literature on brain tumours much has been learnt about optimising management of patients with malignant gliomas. Transferring this information into good practice is important to avoid some of the potential pitfalls of therapeutic nihilism. Conversely, in many patients the omission of active treatments may be less detrimental than problems related to futile intensive therapies. Optimal management can range from using appropriate palliative strategies by a conscientious neurooncologist based in a general hospital to using novel, but unproven, treatments in the setting of a multidisciplinary cancer centre. What, therefore, should determine and influence decision making in the management of patients thought to have a malignant glioma?

Towards a diagnosis: diagnostic neuroradiology

The increasingly widespread use of MRI for neuroradiological diagnosis has enabled identification and diagnosis of focal lesions of the brain often when such lesions would not be visualised with CT. From the surgical perspective this has been particularly useful for the investigation of patients with no clinical abnormality but a history of adult onset seizures. A proportion of these patients with apparently innocuous focal lesions, as well as many patients diagnosed by CT to have low grade astrocytomas, will harbour an anaplastic astrocytoma when histological diagnosis is obtained. The difference between low grade astrocytoma and anaplastic astrocytoma is important as management strategies are different. Most malignant gliomas are, at the time of presentation with focal symptomatology, detectable by CT. Gadolinium enhanced MRI does, however, often show either a more extensive or multifocal lesion when compared with CT. Patients with malignant gliomas can present with quite variable symptomatology, and such neoplasms may also radiologically mimick the gamut of brain neuropathologies. A high index of suspicion must therefore be maintained to avoid the albeit low risk <4% of misdiagnosing a benign non-neoplastic lesion as malignant glioma.

In some patients tissue confirmation of diagnosis of malignant glioma may not be appropriate. This cohort includes patients in whom the history is of a progressive neurological deficit, neuroradiological studies show characteristic features suggestive of a glioblastoma, and clinical examination discloses major neurological or cognitive deficits and disability. Although most such patients will be elderly, biological age and both the patient’s and their family’s opinions must be considered and reasons for a non-interventional management approach explained. The rationale for this nihilistic but pragmatic approach is based on the very poor prognosis, both for life expectancy and functional improvement even after multimodality therapy, associated with glioblastoma in the elderly patient (>60 years) who presents with poor functional status. In this cohort judicious use of glucocorticoid treatment will optimise neurological function. Good primary medical practice and the use of home nursing and hospice care provide best management for most of these patients. The facility for additional neurooncological follow up should, however, be retained as an option as even without treatment some of these patients survive longer than expected, and are at risk of major steroid related complications and even misdiagnosis.

Making the diagnosis: surgical approaches

Perhaps one of the major recent advances in the management of patients with malignant brain tumours has been the decrease in morbidity and mortality associated with both biopsy and major cytoreductive surgery. Before the advent of image-guided stereotactic biopsy techniques diagnostic surgery was often associated with unacceptable levels of morbidity, mortality, and failure to make a definite pathological diagnosis. Nowadays with MR or CT guidance systems the morbidity of stereotactic biopsy...
of lesions anywhere in the brain, even in the frail and elderly, is usually <5% and the mortality <1%.14,15 In many cases the 30 day morbidity associated with biopsy is either transient or related to the rapid progression of the infiltrative potential of malignant gliomas.2 The proper- 
nization of the diagnosis of malignant glioma has been emphasised in several papers particularly when there may be neuroradiological uncertainty between diagnoses of malignant glioma, metastatic lesion, abscess, inflamma-
tory lesion, or other contrast enhancing neuropathologi-
cal processes.2,17 An experienced neuroradiologist, provided with appropriate clinical information, will cor-
rectly diagnose 95% of CT imaged malignant brain tumours.12 Therefore in many cases biopsy confirmation of a diagnosis of malignant glioma could be argued to have added little to patient management. Tissue diagno-
sis, however, where appropriately indicated, facilitates making decisions to employ interventionial therapies as patients with anaplastic astrocytoma and anaplastic oligodendroglia respond significantly better to interven-
tional treatments than those with glioblastoma.2,5,6,18-21 In both middle aged and elderly patients, tissue diagnosis allows realistic discussion with the patient and their immediate families about both prognosis and subsequent management decisions.

Whether cytoreductive surgery is helpful in malignant glioma depends on the outcome measured. Certainly signs and symptoms related to raised intracranial pres-
sure can be relieved, seizure frequency and intensity reduced, and many focal neurological deficits improved.2,5,12,20,24 Requirements for corticosteroid treatment, which can be a cause of significant morbidity in patients with brain tumours,14 are also either considerably reduced or abolished postoperatively. With the technical facilities and adjuncts that are now available, such as three dimen-
sional and multiplanar reconstructions of MRI, high quality operating microscopes, precision microin-
strumentation, frame based or frameless stereotactic cran-
ootomy and lesion localisation techniques,25 and awake craniotomy with cortical mapping techniques,26 cytore-
ductive surgery can be performed safely and effectively.
The morbidity associated with such procedures will be determined by the experience, skill of the surgeon, and neuro-oncologist. As there is a fine balance between improving and worsening neurological function with cytoreductive surgery it is imperative, as these patients have an incurable disease with a poor natural history, that iatrogenic disability is minimised.

The contribution of cytoreductive surgery to improv-
ing median survival times is controversial.2,5 In some studies extensive surgical resection of malignant gial tumours has been shown to be an independent prognostic variable2,4 whereas in others it is not a significant fac-
tor.2,28 Unfortunately much of the medical literature on the role of surgery for malignant glioma is unsatisfactory as series are often retrospective, not randomised between biopsy and major resection, not stratified for the impor-
tant independent prognostic variables such as age, perfor-
mance, and neuropathological subgroup, and often contain inadequate numbers for appropriate statistical analysis.2 None the less any benefits of cytoreductive surgery probably become less with both increasing age of the patient and increasing tumour malignancy.2,15 The limited survival benefit bestowed by even the most exist-
ing cytoreductive operation for malignant glioma, and particularly glioblastoma, is related to the invasive and infiltrative potential of malignant glioma.2 These proper-
ties seem related to the production of plasminogen activ-
ators, matrix metalloproteinases, and the secretion of certain growth factors, all of which enhance malignant cell migration through the extracellular brain matrix.29 Generally peritumoral invasion extends for 2 cm beyond either the macroscopic tumour margin or the borders defined by enhanced CT.7 In most locations the likeli-
hood of iatrogenic brain dysfunction prohibits excision of infiltrated peritumorous brain. Even when extensive peri-
tumorous brain resection has been undertaken tumour recurrence at the margin of resection is inevitable.7,24

Management after diagnosis: lessons from clinical trials

External beam brain irradiation remains the standard treatment in the management of malignant gliomas. An optimal total dose of 60 Gy in 30 fractions is conven-
tional.2,30 In many prospective studies, of mixed anaplas-
tic astrocytoma and glioblastoma cohorts, such treatment will have contributed to a median survival time of between nine and 11 months.25 The addition of a radiosensitiser during radiotherapy has not significantly improved survival times31,32 and doses >60 Gy are associated with a high incidence of acute and short term neuro-
ological side affects and later cerebral radionecrosis with no benefit in either median or longer term survival.33 Since the 1970s chemotheraphy using a nitrosourea has also been widely used either as adjuvant therapy after radiotherapy or after glioma recurrence.3,5-7,20 Meta-
analysis suggests a small survival advantage can be obtained with adjuvant chemotherapy.34 Recent studies suggest single agent nitrosourea therapy is as effective as multi agent therapy.2,4,15,22 Responses, in terms of median sur-
ival time and percentage of survivors at two years, to radiotherapy and chemotherapy, are better in patients with either an anaplastic oligodendroglia or an anaplastic astrocytoma than those with glioblastomas. Review of data from different prospective, randomised clinical trials has shown that patients with anaplastic astrocytoma have median survival times from 36 months6 to two years18 compared with a median 8-6 months and 10% two year survivors for patients with glioblastoma.4,10,21 Other favourable prognostic variables are younger age, good performance status, and a previous history of seizures.1,5,12 Using these factors predictions about survival can be made.

Disease relapse after both radiotherapy and chemotherapy is invariably due to recurrence within 2 cm of the original lesion.2,7,30 Why do these treatments, which theoretically should sterilise infiltrated peritumorous brain, not give better results? Studies of the radiobiology of malignant glioma cell lines in vitro show that they have an inherently high radioresistance, with a large capacity for DNA repair which can continue without major slow-
ing of the cell cycling time (Ross G, personal communi-
cation). Failure of chemotherapy for malignant gliomas is probably related to both inherent tumour cell chemore-
sistance and failure of drug delivery.1,5,12 The blood-brain barrier can limit transport of large molecular weight, polarised, non-lipophilic agents into peritumorous brain; however, in the tumour interstitium there is no compara-
ble biophysical barrier.36 Many glioma cell lines are inher-ently resistant to doses of chemotherapeutic agents that may be attained in vivo and even non-conventional high dose therapy given with bone marrow rescue.7 Such resis-
tance is related to drug efflux systems such as the mul-
tidrug resistance (mdr) gene, and the enzyme O6-alkylguanine-DNA alkyltransferase, which limits the toxicity of alkylating agents.37 A multiplicity of novel chemotherapeutic agents and drug regimens have been given in phase 2 and phase 3 studies to patients with relapsed malignant glioma.38 Despite some initial promise
for some of these drugs nitrosoureas remain as effective as these novel agents. Therapeutic approaches designed to improve the delivery to the tumour include suprapthalomical intracarotid arterial infusion, 
orsmic opening of the blood-brain barrier, and the use of implantable polyanhydride polymers impregnated with chemotherapeutic agents.
Results are variable and require cautious interpretation.

Interstitial radiotherapy using stereotactically placed catheters after-loaded with radioactive seeds can contribute to prolongation of survival in selected patients with recurrent disease. Interstitial brachytherapy is, however, associated with foci radiation that often requires steroid treatment, or resection, or both. Clinical trials are currently evaluating the role of interstitial brachytherapy, as an adjunct to external beam radiotherapy in both the primary management and recurrence of malignant glioma. Other studies have considered the roles of hyperfractionated external beam radiation therapy treatment regimens, hyperthermia, and the role of stereotactic radiosurgery using either the gamma knife or a linear accelerator. Unfortunately, the preliminary results with stereotactic radiosurgery for malignant gliomas are disappointing. None of the new approaches, to treatment of brain tumours is the use of suicide genes, such as herpes simplex thymidine kinase (HSV-tk) transfection into tumour cells using a retroviral vector. The transfected cells are rendered sensitive to the cytotoxic effects of gancyclovir. Although this paradigm has worked well in rodent models of brain tumour, the results of the initial clinical studies in humans have been disappointing (Oldfield E, personal communication). Further work is required to improve both the methodology and efficiency of gene transfection of glioma cells and the selection of genes to be used. Whether these problems are surmountable or whether gene therapy for malignant gliomas will prove as disappointing as immunomodulative therapy and monoclonal antibody therapy awaits further studies.

Overall, when reviewing series of different management strategies in patients with malignant brain tumour, it is important to remember that these series report patients who are selected for the studies because of their good prognostic features. An audit of practice in south-east Scotland, which is served by a dedicated neuro-oncology service, showed that only 40% of patients with malignant glioma ever receive either surgery or radiotherapy. Furthermore, there were often significant delays between diagnosis and treatment. Selection of a patient for surgery, or even neuro-oncological referral, depends on many factors including their clinical condition at the time of neuroradiological imaging, the interpretation of the neuroradiological report, the knowledge of the referring physician, the attitudes of the local oncological and neurosurgical services to interventional neuro-oncology, and the desires of the patients and their immediate families. Management of the patients not referred to a neuro-oncological service is as important as those undergoing intensive therapies. Access to written information, and time for explanation of the disorder with their family and reasons for management decisions form an important part of the basic care of patients with malignant glioma. Because cure of malignant gliomas is often impossible therapeutic endeavours should be primarily aimed at improving the patient's quality of life. Quality of life issues are becoming increasingly recognised as impor-

tant in patients with malignant gliomas. Although this is a difficult concept to assess studies using self report questionnaires assessing "well being" have identified freedom from depression, an active social life, energy, and fewer symptoms as being important. The commonly used Karnofsky performance scale was found to be heavily influenced by age and not related to "well being" even though patients had a high Karnofsky performance score. With the increasing demand for evidence-based medicine it is likely that there will be an intensification of research in these areas and a long overdue expansion of support and caring facilities for patients with malignant brain tumours.

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10 Cairncross JG, Lapierre NJ. Low grade glioma: to treat or not to treat? J Neurosurg 1989;70:1239-46.


NEUROLOGICAL STAMP

Willow

Two thousand, four hundred years ago Hippocrates recommended chewing willow leaves for analgesia during childbirth and for postpartum fever. Pliny in Rome in the first century AD prescribed the bark of the poplar (which is also a member of the willow (salix) family) for sciatic pain.

In the 1830s salicin and its derivative salicylic acid were isolated from white willow and various other plants. In the 1870s, salicylic acid was synthesised. Felix Hoffman, a chemist at the Bayer Pharmaceuticals Company in Germany later produced a modified form of salicylic acid, the acetyl derivative, which was effective against fever and arthritic pain. Its antithrombotic properties were described in the 1940s. The name aspirin came from the Spiraea plant, one of the other sources of salicylic acid. The prefix a was added to signify acetyl. Aspirin contains no willow derivatives and is entirely synthetic.

A row of willows is shown on a stamp issued in 1973 depicting Swedish landscapes (Stanley Gibbons 736, Scott 158).

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34 Stenning SP, Friedman LS, Blehen NM. An overview of published results from randomized studies of nitrosoureas in primary high grade malignant glioma. Br J Cancer 1987;56:89–90.