What to do with the patient and the scan shows

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A TYPICAL PATIENT
A 28-year-old lady was brought into the emergency department having had two generalized tonic–clonic seizures. These terminated spontaneously and by the next day she was feeling back to normal apart from a mild headache. She recalled involuntary head turning to the left just before blacking out. Postictally there was no neurological deficit, and there was no earlier history of headaches. She was otherwise fit and well. Her brain CT scan showed a large low-density space-occupying lesion in the right frontal lobe, which did not enhance with contrast, suggestive of a glioma, probably low-grade (Fig. 1).

At this point the key issues are:
- How reliable is CT/MR scanning in detecting and grading gliomas?
- What are the risks, benefits and limitations of stereotactic biopsy?
- When is it appropriate to recommend gross total resection?
- If a biopsy or resection is done and shows a low grade glioma, what is the evidence that treatment with radiotherapy improves overall outcome?
- If a biopsy or resection shows a high-grade glioma, what further treatment should be recommended – radiotherapy or chemotherapy?

BACKGROUND
Gliomas are the most frequent type of primary brain tumour with an incidence of about 20 per 100 000 population per annum. They are classified and graded by the World Health Organization (WHO) on the basis of their morphological features alone (Table 1). WHO Grades I and II are low-grade gliomas while Grades III and IV

Figure 1 Pre- and post-contrast brain CT scan showing a large non-enhancing homogeneous low-density mass in the right frontal lobe of a 28-year-old woman presenting with seizures. A subsequent MR scan confirmed that this was a non-enhancing tumour and the decision was made to rescan her after 3 months.
are high-grade. Low-grade gliomas account for about one-third of all gliomas and are particularly frequent in younger patients. Grade I tumours occur almost exclusively in children while Grade II tumours most frequently present in young adults. Gliomas account for 80% of tumour-associated epilepsy. Seizures are the second most common presenting symptom of intracranial tumours after headache, occurring in 21% of patients (Grant 2004), and are more likely than headache to be the presenting complaint of a low grade glioma. Therefore, an adult presenting with seizures and a suspected tumour on the CT scan is more likely to have a low-grade glioma (WHO Grade II astrocytoma, oligodendroglioma or mixed glioma) than a high-grade tumour.

By definition, a low-grade glioma is slow growing and patients have a median survival of many years, dependent mainly on histological subtype. However, in most cases, these tumours undergo malignant transformation to a high-grade glioma, at an unpredictable time in their natural history. The median survival for patients with WHO Grade II gliomas varies from 5 to 7 years for astrocytomas, to 16 years for oligodendrogliomas (Olson et al. 2000), and somewhere in between for mixed gliomas (oligastrocytomas). In contrast, the median survival for a patient with a malignant glioma is about 1 year for a glioblastoma (WHO Grade IV) and 2–3 years for an anaplastic astrocytoma (WHO Grade III), depending on age and performance status with young fit patients surviving considerably longer than older frail patients.

The appropriate management of patients with intracranial tumours therefore relies on accurate diagnosis of tumour type. It is important to identify the patient whose scan suggests a high-grade glioma and refer urgently to neurosurgery for a tissue diagnosis because adjuvant treatment, particularly radiotherapy, improves survival over supportive care alone (Walker et al. 1980) and this should be started as soon as possible in appropriate patients. In fact only one paper addresses this specific question but it did show that a longer waiting time from presentation to radiotherapy department to treatment was a significant predictor of early death (Do et al. 2000). Moreover, given the known doubling times of high-grade gliomas, it seems reasonable to advocate treatment as soon as possible.

The management of low-grade gliomas is more controversial and the correct decision, if there is such thing as a correct decision in this context, should only be made after considering

Table 1 WHO Classification of Gliomas

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<tr>
<th>Tumour Type</th>
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<td>Astrocytic tumours</td>
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<td>Pilocytic astrocytoma</td>
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<td>Diffuse astrocytoma</td>
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<td>Anaplastic astrocytoma</td>
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<td>Glioblastoma</td>
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<td>Oligodendroglial tumours</td>
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<td>Oligodendroglioma</td>
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<td>Anaplastic oligodendroglioma</td>
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<td>Mixed gliomas</td>
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<td>Oligastrocytoma</td>
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<td>Anaplastic oligoastrocytoma</td>
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the clinical presentation, the anatomical location of the tumour, the opinions of the neurologist and neurosurgeon, and the feelings of the patient. Ideally this decision-making process should take place within the setting of a neuro-oncology multidisciplinary team meeting made up of neurosurgeons, neurologists, neuroradiologists, neuropathologists, clinical oncologists and clinical nurse specialists.

**HOW RELIABLE IS CT SCANNING IN DETECTING AND GRADING GLIOMAS?**

A number of features help predict the grade of an intrinsic tumour seen on a CT scan. The patient's age gives some indication because adults with low-grade glioma generally present in the third or fourth decades with seizures, while adults with high-grade gliomas more commonly present in late-middle or older age with symptoms and signs of raised intracranial pressure, or a short history of progressive focal deficit or cognitive decline. Certain radiological features influence the likely diagnosis. The well-known butterfly glioma develops when malignant tumour cells infiltrate the white matter tracts of the corpus callosum. If present, bone remodelling is more likely to have occurred in response to a slowly growing tumour (Fig. 2), and intratumoural calcification suggests that the tumour is an oligodendrogloma (Fig. 3).

The overall diagnostic error rate for neuroradiological interpretation for all brain tumours (vs. other pathologies) is less than 5%, but 10% of CT scans are normal, usually when the scan is unenhanced and the tumour is in the temporal lobe. To assess the accuracy with which CT scanning predicts tumour histology, general and neuroradiologists in three Scottish neuroscience centres were asked to give their best guess tumour diagnosis after reviewing the CT scans of 221 patients presenting with a solitary, supratentorial intracerebral tumour who then went on to have a definitive pathological diagnosis. Tumours were prospectively classified as 'malignant glioma', 'low-grade glioma' or 'metastasis' in 199 cases. The sensitivity of CT for low-grade glioma was only 0.44 although the specificity was 0.9. The positive predictive value was only 0.35 implying a false positive diagnosis rate of 65%, and most frequently due to the misdiagnosis of a malignant glioma (Bell et al. 2002). This latter problem is widely recognized and is generally due to lack of contrast enhancement in the lesion. This was clearly shown in a study of 314 unselected patients with gliomas, of whom nearly 20% lacked contrast enhancement and, of these, approximately one-third were malignant, particularly in older patients (Scott et al. 2002).

The comparison of CT with pathology is complicated by tumour heterogeneity, a characteristic pathological feature frequently found in resection specimens of gliomas, where there may be small foci of anaplasia in an otherwise low-grade tumour.

**MR IMAGING AND THE DETECTION OF GLIOMAS**

MRI is now universally regarded as the imaging modality of choice in view of its greater anatomical resolution than CT, its superior ability to differentiate pathological tissue from normal brain, and the higher sensitivity to the presence of tumour. Low-grade gliomas appear as high signal mass lesions on T2 and FLAIR sequences (Fig. 2), and intratumoural calcification suggests that the tumour is an oligodendrogloma (Fig. 3).

As a general rule, on MRI low-grade gliomas are non-enhancing or only faintly enhancing while high-grade gliomas enhance avidly, with an irregular outline, necrotic centre and peritumoural vasogenic oedema.
quences and as low signal on T1 sequences. Calcification is usually seen as T1 shortening. Very low-grade gliomas (WHO Grade I), e.g. pilocytic astrocytomas, usually appear as well circumscribed cystic tumours with a mural enhancing nodule. In contrast to their higher-grade counterparts, they are relatively benign, extremely slow-growing and potentially curable by surgery alone.

As a general rule, low-grade gliomas are non-enhancing or only faintly enhancing while high-grade gliomas enhance avidly, with an irregular outline, necrotic centre and peritumoral vasogenic oedema (Fig. 4). The presence of enhancement in a low-grade glioma is associated with a worse prognosis in terms of time to progression and overall survival (Vaquero et al. 2002).

However, even MRI scanning may give misleading information. In a study of 20 consecutive adults suspected of having a low-grade glioma on imaging criteria, only 10 in fact had low-grade tumours—nine had anaplastic astrocytomas and one had encephalitis (Kondziolka et al. 1993). This was a retrospective study from a single tertiary referral centre where the pathology was already known at the time the radiologists were asked for their diagnosis. It does not tally with our own experience where over 90% of tumours that appear low-grade on imaging are confirmed to be so pathologically. This difference may also reflect the lack of clear criteria for distinguishing a Grade I glioma from a Grade III anaplastic glioma, particularly if a tumour is ‘upgraded’ solely on the presence of one or two mitoses on histology.

There have been a number of attempts to introduce multiparametric imaging modalities to provide additional information over and above that obtained from conventional sequences. These include single voxel MR spectroscopy, Chemical Shift Imaging, Diffusion Weighted and Perfusion Imaging (Rees 2003). But at present these techniques are not widely available on a routine basis and are therefore unlikely to influence clinical practice outside a few specialist centres. While they are helpful in predicting tumour grade, they do not provide clear-cut information about the tumour type and therefore do not avoid the need for a tissue diagnosis.

Functional metabolic imaging with Single Photon Emission Tomography (SPET) and Positron Emission Tomography (PET) can also help distinguish low-grade from high-grade tumours but suffers from lack of spatial resolution. Most published studies have based their conclusions on small numbers of patients and in our experience these techniques may give misleading information. SPET and PET are now mainly used when biopsy is contraindicated or, after treatment, when there is a question as to whether clinical and radiological progression is due to recurrent disease or radiation necrosis.

Because of the likelihood of increasing grade in older patients and the relative limitations of scanning in predicting grade and type, it is clearly important to obtain a tissue diagnosis, particularly in those patients who are more than 50 years old at presentation, where there is a higher probability of missing a high-grade glioma. For younger patients, less than about 50 years old, who are more likely to be harbouring a low-grade glioma, and who are, apart from epilepsy, otherwise asymptomatic, our practice is to rescan after a relatively short interval (e.g. 3 months) to determine the biological activity of the lesion (in all other cases, an early biopsy is recommended). Clearly, growth over that time period would be more compatible with a high-grade tumour and so lead to neurosurgical referral. If the second scan is unchanged and the patient remains well, it is reasonable to adopt a watch-and-wait policy with regular MR scans and clinical monitoring although the precise scanning interval will depend on local resources. It seems prudent to scan every 6 months and if, after say 2 years, the tumour size is unchanged or only slightly larger, the interval can be increased to yearly.

WHAT ARE THE RISKS, BENEFITS AND LIMITATIONS OF STEREOTACTIC BIOPSY?
Stereotactic surgery of the brain, allowing millimetric accuracy in targeting deep-seated brain structures, was introduced by Spiegel & Wycis in 1947 (see Gildenberg 2004) and has been developed further with the introduction of axial imaging techniques over the last 30 years. Morbidity and mortality are minimal with a risk of less than 5% and 1%, respectively, in most series. We quote a major complication risk of 1 in 300 (death, permanent neurological disability), a minor compli-
cation risk of 2–3% (haematoma, infection) and an inconclusive diagnosis risk of 6% (Revesz et al. 1993).

Stereotactic biopsy has two important roles - firstly to provide an accurate indication of the nature and grade of the tumour, and secondly to avoid misdiagnosis of a radiological abnormality as a neoplasm when the differential diagnosis includes a non-neoplastic process such as abscess. There have been relatively few studies comparing the diagnostic accuracy of stereotactic biopsies with the final histology of tumour specimens from subsequent resection of the lesion within a short time span. In a retrospective study, 81 patients underwent tumour resection at the M D Anderson Cancer Center (MDACC) within 60 days of an initial stereotactic biopsy. Biopsy reports, mainly provided by pathologists at other institutions, differed from resection histopathology in about half the cases as reported by pathologists from MDACC. However, this discrepancy fell to about one-third when both biopsy and resection pathologies were reviewed by MDACC pathologists, clearly reflecting the variability of interpretation of glial tumours by different pathologists (Jackson et al. 2001).

In a second series of 43 patients treated at Duke University, North Carolina the biopsy diagnosis was consistent with the resection diagnosis in 79% of cases and allowed appropriate management in 96% of cases (McGirt et al. 2003).

WHEN IS IT APPROPRIATE TO OFFER A GROSS TOTAL RESECTION?

There are three goals in tumour surgery: tissue diagnosis, reduction of symptomatic mass effect, and ‘curative’ tumour resection. The first goal can be achieved with minimal risk and good accuracy by stereotactic biopsy, as we have already discussed. The clearest indication for resective surgery is the alleviation of local mass effect from the tumour, the likely improvement of neurological function as a result, and the prevention of herniation. This is rarely an issue in patients with low grade glioma. Therefore, the greatest difficulty surgeons currently face is the lack of evidence required to make a rational decision as to whether the potential benefits of radical resection of a suspected low-grade glioma justify the risks of surgery.

There is no good evidence supporting the benefit of resective surgery because there are no randomised controlled trials. The interpretation of retrospective studies is limited by selection bias as well as by the fact that many series have included patients with a variety of low-grade pathologies with diverse natural histories. However, recent publications point towards a tendency to lower recurrence rates and improved survival with radical resection (Winn & Youmans 2004). Residual tumour volume after resection seems to be more important than the proportion of tumour removed in achieving this benefit (Berger et al. 1994). However surgeons have traditionally been poor at estimating the extent of tumour resection. Nowadays new technologies such as intraoperative MRI, combined with histological sampling of resection margins, provide a gold standard in assessing totality of tumour resection.

The risks of surgery depend on the location of the lesion. Patients with deep-seated lesions, or lesions close to eloquent cortex, such as Broca’s area or the motor strip, are at greatest risk. There are numerous methods to lessen surgical risks in such patients. Pre-operative functional imaging using PET or functional MRI can define areas of eloquent cortex and establish the relation of such areas to the tumour. Neuro-navigation involves the fusing of anatomical landmarks during surgery with landmarks on preoperative imaging. This allows software to provide a ‘head-up’ display of pre-operative anatomical and functional imaging superimposed on the surgical field. Information not immediately obvious in the surgical field, such as radiological boundaries of a diffuse infiltrative tumour, or the exact position of eloquent cortex such as the motor strip, is then available to the surgeon and can influence the extent of resection. Intra-operative physiological mapping, ‘awake’ craniotomy and intraoperative MRI are all techniques that are being employed to maximise resection of tumour whilst minimizing risk of neurological deficit.

Radical resection of tumours in non-dominant, polar regions (anterior frontal, anterior temporal lobes) can be performed with minor risk of surgical morbidity and is probably the treatment of choice. In the absence of Class I evidence (one or more well-designed randomised, controlled trials) to support its benefits, radical surgery for tumours in other locations can only be viewed as one option. Although there are no clear benefits of radical resection in published studies, there is a trend to improved outcomes.
Debulking surgery is appropriate if there is raised intracranial pressure or progressive focal deficit. Otherwise it is reasonable to make a tissue diagnosis with biopsy alone and adopt a ‘wait and see’ policy with low-grade lesions.

54 Gy in the 6 weeks immediately after surgery or to no treatment until tumour progression. After a median follow-up of 5 years, the irradiated group showed a significant improvement in time to progression but not in overall survival or neurological functioning (Karim et al. 2002). One reason for this paradox is that once a patient who has already received radiotherapy has progressed, the only available treatment options are further surgery, chemotherapy or experimental therapy, all of which are inferior to radiotherapy in the control of progression to high-grade gliomas.

This trial raises the important question as to whether radiotherapy has any role in newly diagnosed low-grade glioma if overall survival and neurological function are not improved, particularly as there are concerns about long-term neurocognitive sequelae and the risk of second tumours after brain radiotherapy.

In our opinion, the best strategy is to determine the earliest stages of malignant transformation with serial MRI studies and then treat with radiotherapy before neurological deterioration occurs. The appearance of a new or enlarging area of gadolinium enhancement, marked progression of signal change indicating rapid tumour growth, or the development of a new focal deficit or symptoms of raised intracranial pressure would all be indications for biopsy and/or resection followed by adjuvant radiotherapy if there was pathological confirmation of malignant transformation. In the situation where there is a newly enhancing region in an otherwise stable tumour, the surgeon should attempt to biopsy the enhancing region, as this may be the only focus of malignant transformation in an otherwise low-grade tumour.

Radiotherapy has been used in stable tumours causing medically intractable epilepsy. Although there is a limited literature evaluating this approach, our experience suggests that about 75% of patients experience improved seizure control.

It is therefore inappropriate to suggest that all such surgery should stop. It is also inappropriate to suggest that all patients should have radical resection. Therefore, in the absence of evidence either way, management should be on an individual level with open discussion with the patient, and tailored to the individual patient and practice of the clinician (Keeles et al. 2001). As such, surgery should probably only be performed in centres with access to the techniques described above and, ideally, within a randomised trial of surgery vs. conservative management (Whittle 1999).

The lack of any clear advantage from resective surgery for low-grade gliomas is further suggested by a study of almost 1000 adult patients in whom the median survival after biopsy alone was 6.4 years, after subtotal tumour resection 6.8 years, and after gross-total tumour resection 7.6 years (Johannesen et al. 2003). This difference was not statistically significant and tends to support the opinion that it is equally reasonable to adopt a conservative ‘wait and see’ policy for most patients who do not have clinical or radiological features suggestive of progression, as originally suggested 10 years ago (Recht et al. 1992), and for patients whose tumours involve eloquent regions of the brain.

In essence, therefore it is appropriate to consider resection for patients with non-dominant hemisphere polar low-grade gliomas. In all other patients the decision to resect will depend on the location of the tumour, the neurosurgical expertise available, and the opinion of the neurologist and neurosurgeon regarding the strength of evidence in favour of resection. Debulking surgery is appropriate if there is raised intracranial pressure or progressive focal deficit. Otherwise it is reasonable to make a tissue diagnosis with biopsy alone and adopt a ‘wait and see’ policy with low-grade lesions.

**IF A BIOPSY OR RESECTION SHOWS A LOW GRADE GLIOMA, WHAT IS THE EVIDENCE THAT EARLY RADIOTHERAPY IMPROVES OVERALL OUTCOME?**

Unfortunately there is no good evidence that early radiotherapy improves overall outcome. Two studies, one from Europe (Karim et al. 1996) and the other from the United States (Shaw et al. 2002), have both shown that the dose of radiation does not influence survival, nor does the timing. Over 300 patients with pathologically diagnosed Grade II gliomas were randomized to either radiotherapy at a dose of
IF A BIOPSY OR RESECTION SHOWS A HIGH-GRADE GLIOMA, WHAT FURTHER TREATMENT SHOULD BE RECOMMENDED?

The treatment for high-grade gliomas has advanced considerably over the last year or so, particularly with increasing use of systemic and interstitial chemotherapy. Unlike surgery, radiotherapy has been shown in two separate randomised trials to prolong survival in patients with malignant gliomas. There have been many attempts to increase the radiation dose to the tumour while minimizing the dose to surrounding normal tissue, but none have been more successful than a standard course of external beam radiation (60 Gy) delivered to the tumour plus a 2–3 cm margin of normal tissue. The use of concomitant (at the same time as radiotherapy) and adjuvant (after the completion of radiotherapy) chemotherapy with the oral alkylating agent, temozolomide, has improved the median survival of patients with glioblastoma from 12 months to 15 months and the 2-year survival from 8% to 26% (Stupp et al. 2005). Similarly, there is evidence from a recently published randomised trial that interstitial chemotherapy with biodegradable polymers containing BCNU 1,3-bis (2-chloroethyl)-1-nitrosourea (Gliadel® wafers, Link Pharmaceuticals Ltd, Horsham, UK) inserted into the resection cavity in patients with primary malignant gliomas can prolong survival from 11.6 to 13.9 months even after adjusting for other factors that influence survival (Westphal et al. 2003).

CONCLUSIONS

There are many controversies and difficulties in managing patients with a suspected low-grade glioma on imaging. Management options should ideally be discussed within a structured multidisciplinary meeting attended by neurologists, neurosurgeons, neuroradiologists, clinical and medical oncologists, and neuropathologists to provide each patient with an informed opinion based on the best evidence available, and tailored to individual circumstances. Figure 5 is a suggested algorithm for our approach to diagnosis and treatment.

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**Figure 5** Treatment algorithm for suggested management of a patient presenting with a seizure who is found to have a glioma on CT scan.

![Diagram](http://pn.bmj.com/first-published-as-10.1111/j.1474-7766.2006.00287.x-on-1-april-2005.0.png)
PRACTICE POINTS

- The appropriate management of patients with intracranial tumours relies on accurate diagnosis of tumour type.
- MRI is now universally regarded as the imaging modality of choice in view of its greater anatomical resolution than CT, and its superior ability to differentiate pathological tissue from normal brain.
- As a general rule, low-grade gliomas are non-enhancing on MRI or only faintly enhancing, while high-grade gliomas enhance avidly, with an irregular outline, necrotic centre and peritumoural vasogenic oedema.
- For younger patients, who are more likely to be harbouring a low-grade glioma, and who apart from epilepsy are otherwise asymptomatic, we rescan after 3 months to determine the biological activity of the lesion.
- If the repeat scan shows no growth, we rescan at 6-monthly intervals and intervene surgically (biopsy or resection) if there is clinical deterioration (symptoms or signs of new focal deficit or raised intracranial pressure), or radiological evidence of new or progressive contrast enhancement, or significant volume change.
- Stereotactic biopsy allows differentiation of primary intrinsic brain tumours from other pathologies, as well as grading and typing of gliomas, with minimal surgical risk. Grading of intrinsic tumours is essential to formulate a management plan.
- Radical resection is for low-grade tumours in non-dominant, polar regions can be performed with minor risk of surgical morbidity and is probably the treatment of choice for tumours in these locations.
- We only recommend radiotherapy when there is clinical or radiological evidence of malignant transformation, or in medically intractable epilepsy where improvement in seizure control will significantly improve the quality of the patient's life.
- Management options should be discussed within a structured multidisciplinary meeting attended by neurologists, neurosurgeons, neuroradiologists, clinical and medical oncologists, and neuropathologists.

REFERENCES


