

MRI in treatment of adult gliomas

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Diffuse astrocytomas of the adult cerebral hemispheres are unique among tumours in human beings in the extent to which their imaging features are related to histopathological characteristics and clinical behaviour. However, understanding is still restricted about the value of imaging features in the measurement of response and of progression in these tumours. The present approach used in clinical trials, which consists of an anatomical measurement of the enhancing tumour on MRI, has many problems, and might not be acceptable as a surrogate endpoint for survival in patients with glioblastoma who are enrolled in clinical trials. Dynamic imaging techniques, such as capillary permeability mapping, are being used in studies of new drugs that target specific molecular features of gliomas; however, the validity of these techniques has not been elucidated. Diffusion imaging can be valuable for fibre-tract mapping to assist surgical planning and might become useful in measuring early response to treatment in densely cellular tumours. Functional imaging techniques can be used to localise motor, sensory, and language-control areas before surgery. Intraoperative MRI has produced improvements in the extent of tumour resection, and molecular imaging is another technique on the horizon, which could come to have a role in clinical trials in the near future. Thus, as a rapidly expanding sphere of investigation, brain-tumour imaging is producing great excitement. The aim of these new techniques is to aid the identification of more effective treatments.

The introduction of MRI into clinical practice has been among the most important of all advances in the care of patients with brain tumours. The crucial roles of neuro-imaging in neuro-oncology include refinement of preoperative differential diagnosis, precise anatomical localisation for operative planning (figure 1), detection of response to treatment and of tumour progression, and recognition of side-effects that are treatment related. However, there are many unsolved difficulties in the use of MRI in neuro-oncology. New techniques that allow analysis of the chemical composition of tumour tissue, capillary density, and the diffusion of water, have great potential but are not yet well validated. The specialty of molecular imaging is expanding rapidly, although only in the preclinical setting. Here we review the status of these techniques and other issues in neuro-oncology.

Correlation between imaging appearance and histological features of gliomas

Diffuse astrocytomas of adult cerebral hemispheres are unique among tumours in human beings for the scale to which their imaging features relate to clinical behaviour and histopathological characteristics. In low-grade, diffuse, fibrillary astrocytomas (WHO grade II; figure 2) there is mild expansion of the affected brain without evidence of abnormal gadolinium enhancement or substantial surrounding vasogenic oedema. These imaging findings indicate the histopathology of mildly increased cellularity without pronounced angiogenesis. In anaplastic astrocytomas (WHO grade III) there are typically nodular areas of gadolinium enhancement, showing the presence of newly formed blood vessels that have an abnormal blood-brain barrier. These tumours tend to produce moderate expansion of the involved brain regions, because of greater cellular proliferation, and might show evidence of substantial surrounding vasogenic oedema. In glioblastoma multiforme (WHO

grade IV) there is pronounced mass effect and heterogeneous enhancement with centrally non-enhancing regions, which typically relate histologically to sections of necrosis. This tumour type also produces widespread, surrounding T2-weighted hyperintensity as a result of a combination of vasogenic oedema and infiltrating tumour (figure 2).

An important point to recognise is not only that diffuse, infiltrating astrocytomas of the cerebral hemispheres disseminated throughout the brain at the time of diagnosis, but also that this feature is not shown well on imaging. Indeed, precisely because these tumours are infiltrating, intensification of local treatment, such as irradiation, does not substantially improve overall survival.¹

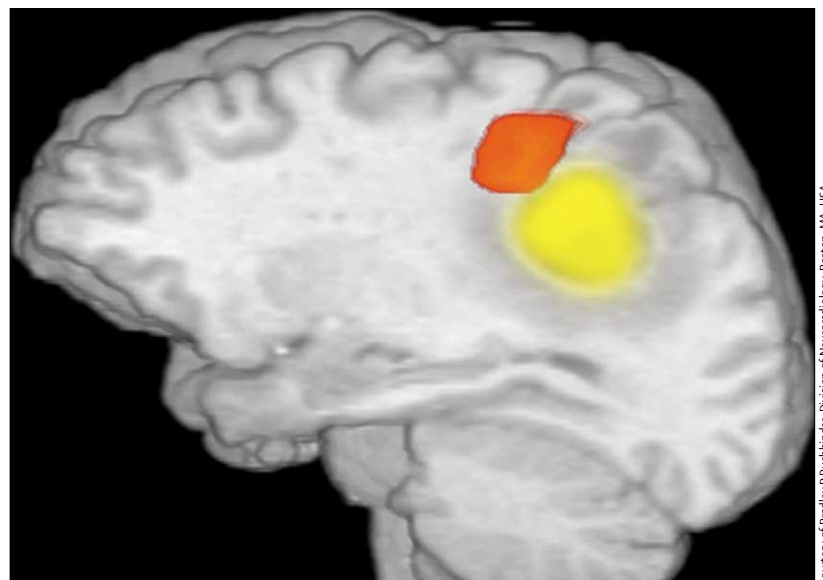


Figure 1: The anatomical association between a tumour (yellow) and the motor-control region for the hand (red) in a patient assessed with blood-oxygenation-level-dependent imaging

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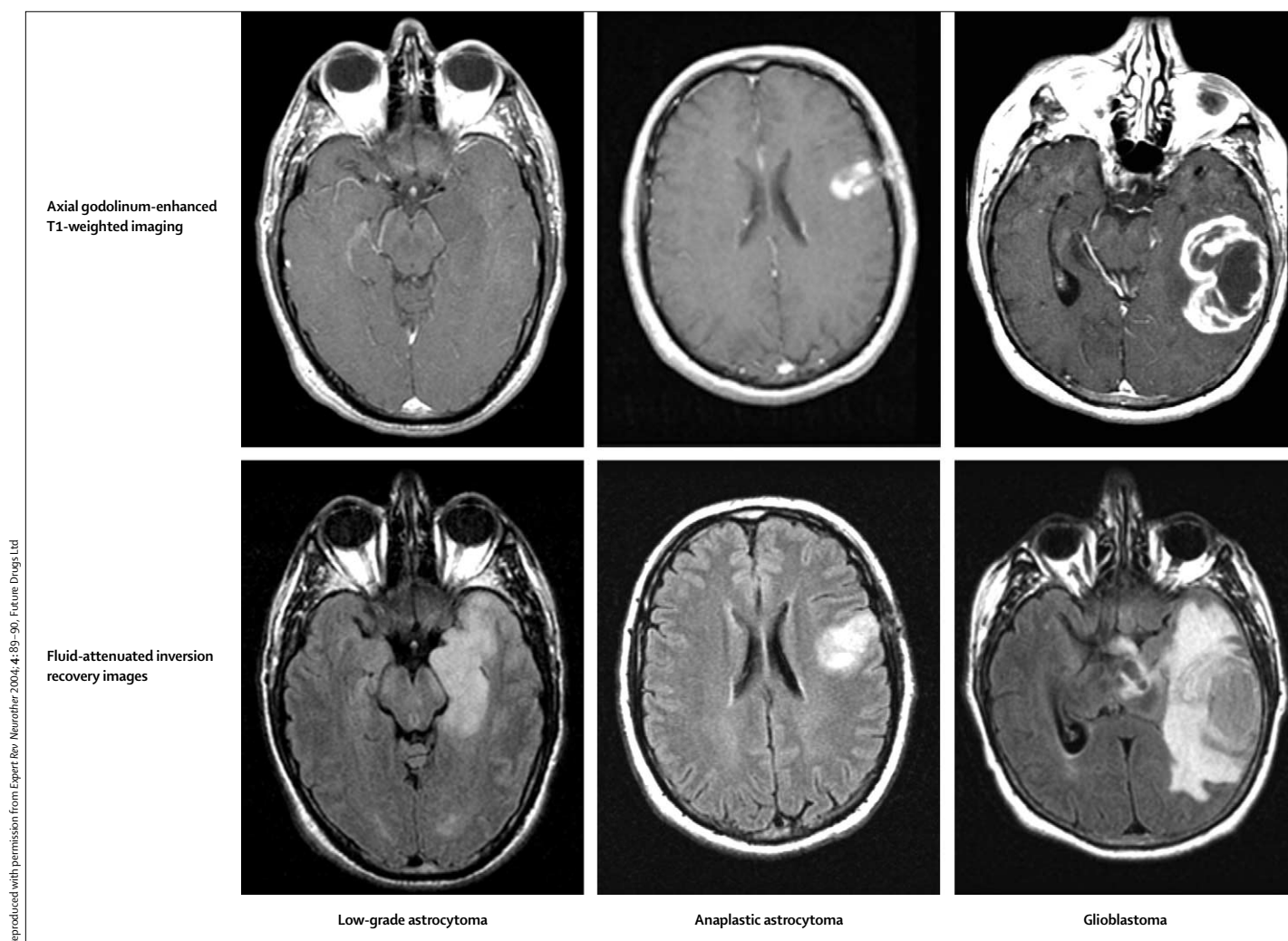


Figure 2: Comparison of imaging findings in low-grade astrocytoma, anaplastic astrocytoma, and glioblastoma

Two other features in imaging of adult gliomas are that the presence of abnormal enhancement in a tumour, shown to be a diffuse astrocytoma, implies the presence of a high-grade tumour, even if the biopsy sample shows low-grade, diffuse, fibrillary astrocytomas. Therefore, enhancing-low-grade tumours should be followed up radiologically with the same frequency as anaplastic astrocytomas. Many low-grade oligodendrogliomas show enhancement without the implication of a higher grade. Alternatively, the absence of enhancement does not imply low-grade histopathology, since a third of non-enhancing, diffuse gliomas in adults are high-grade. The possibility of high-grade histopathology in non-enhancing astrocytomas rises substantially with age, such that by 45 years of age, the chance is 50%.² These facts imply not only that all non-enhancing masses suspected to represent glioma should be biopsied, but also that the intrinsic heterogeneity of gliomas means that imaging tools are needed to help neurosurgeons choose the part

of the tumour for biopsy that will probably contain the high-grade tumour, if present.

Imaging the clinical behaviour of primary brain tumours

Low-grade, diffuse fibrillary astrocytomas have a well-known tendency to become more histologically and clinically severe over time, progressing towards anaplastic astrocytoma and finally glioblastoma multiforme.³⁻⁵ In clinical practice (figure 3A), neurological symptoms lead to the discovery of a non-enhancing mass lesion; the biopsy sample shows a mild rise in cellularity and the absence of mitoses, endothelial proliferation, or necrosis. Months to years later, new neurological symptoms might appear, and neuroimaging shows an area of rapidly growing, contrast-enhancing tumour (figure 3B), which at biopsy shows histopathological changes consistent with anaplastic astrocytoma or glioblastoma multiforme. This development is called anaplastic progression; it results

from a stepwise accumulation of molecular genetic changes within tumour cells. Although the precise numbers are difficult to determine, about 50% of low-grade, diffuse fibrillary astrocytomas undergo radiographically detectable anaplastic progression, with the remainder showing gradual growth as low-grade lesions.⁴

The genetic-progression model is widely accepted for those low-grade, diffuse, fibrillary astrocytomas that progress clinically to glioblastoma multiforme (so-called secondary glioblastoma multiforme). However, astrocytomas have other clinical behaviours. For instance, many younger patients have tumours of this nature that grow gradually without radiographic signs of anaplastic transformation. In distinction, astrocytomas in older patients commonly have features of glioblastoma multiforme at the time of first symptoms, and the low-grade precursor lesion might not be identifiable radiographically or histopathologically. These lesions have been designated *de novo* or primary glioblastoma multiforme (figure 4).^{6,7}

Patients who have glioblastoma multiforme diagnosed after a short period with symptoms, and do not have known, previous, low-grade, diffuse fibrillary astrocytomas (ie, those with primary glioblastoma multiforme), are typically older adults whose tumours overexpress epidermal-growth-factor-receptor and rarely have alterations in the tumour protein P53.^{6,8-10} Conversely, patients whose glioblastoma multiforme arises from a known, low-grade, diffuse fibrillary astrocytoma (ie, secondary glioblastoma multiforme) tend to be younger, and many of these tumours have P53 mutations and loss of heterozygosity of chromosome 17p, but rarely overexpress epidermal-growth-factor-receptor.^{11,12} The dichotomies in the age of the patient, rate of anaplastic progression, and genetic changes in these types of glioblastoma multiforme give strong evidence that distinct genetic pathways produce subsets of gliomas. According to this idea, the tumours of younger patients tend to show anaplastic progression over a period of years, whereas tumours in older patients progress from initial formation to glioblastoma multiforme over months. This idea is directly supported by data showing that low-grade, diffuse fibrillary astrocytomas progress more rapidly to high-grade tumours in older patients.¹³ Although other explanations for tumour behaviour have been proposed,¹⁴ there is little existing or theoretical support for them.

Imaging low-grade gliomas after diagnosis

Patients with low-grade gliomas undergo the maximum possible tumour resection and do not receive adjuvant radiotherapy or chemotherapy unless there are severe related symptoms that restrict their quality of life (eg, intractable seizures) or there is evidence of tumour progression. Thus, the reason for successive imaging surveillance in these patients is the early detection of tumour progression. Low-grade gliomas of the adult

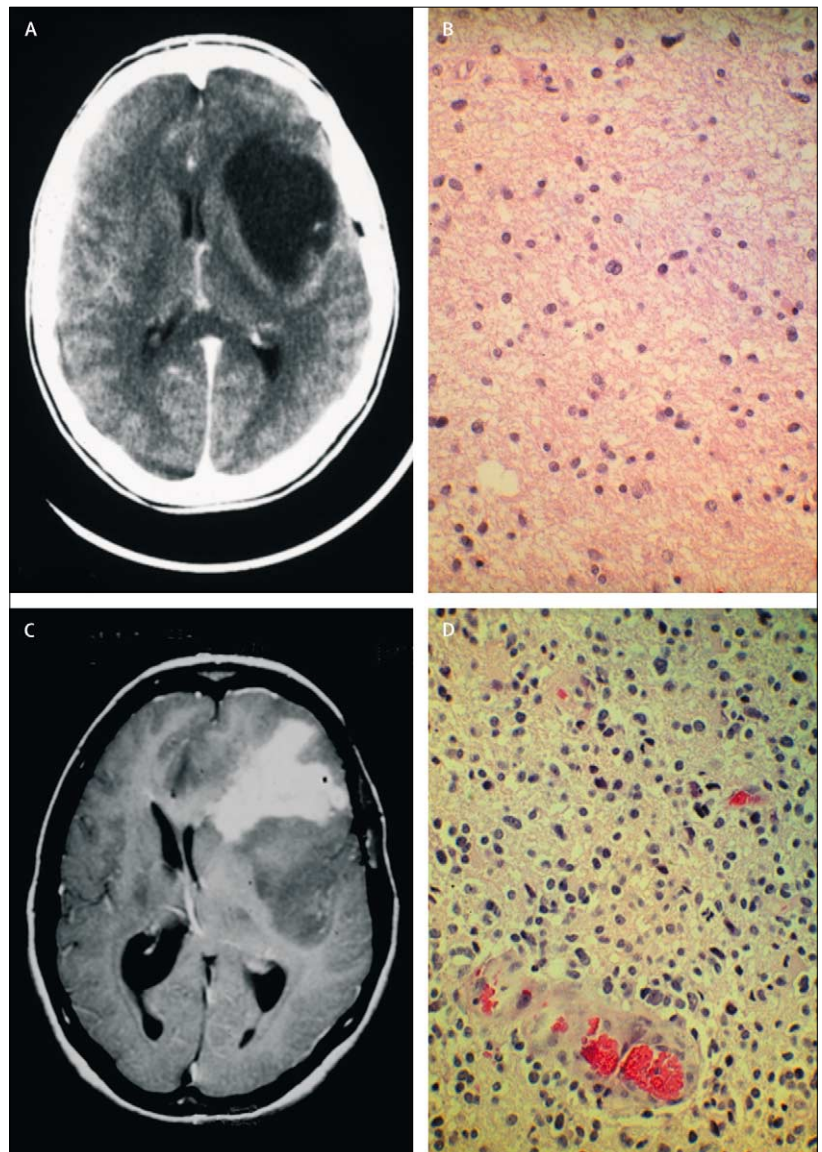


Figure 3: Development of glioblastoma from low-grade glioma

Low-grade glioma shown by a large non-enhancing mass in the left frontal lobe on a CT scan (A) and the biopsy from this lesion, which showed a low-grade oligoastrocytoma (B). Glioblastoma, which had formed from the low-grade glioma over 4 years (C). Most of the low-grade lesion is stable in appearance, but a new contrast-enhancing mass lesion has appeared in the anterior aspect of the lesion. At resection this enhancing region showed the features of glioblastoma (D).

cerebral hemispheres show either gradual enlargement of the non-enhancing mass or anaplastic progression from low-grade to high-grade tumour.

Mandonnet and co-workers¹⁵ found that in untreated, low-grade oligodendrogliomas there is about a 4 mm increase in cross-sectional diameter of the tumour every year (figure 5). Figure 5 shows this pattern of growth in a patient with a left frontal, low-grade oligoastrocytoma who reported increasing severity of seizures with an effect on language function. When compared with the previous study, successive MRI examinations did not

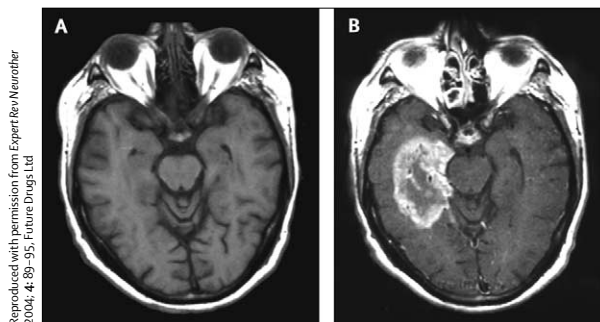


Figure 4: Radiographically demonstrated primary glioblastoma
Patient with healthy MRI results (A) 2 years before a glioblastoma was found (B).

explain the clinical deterioration. However, comparison with an earlier baseline study taken after biopsy showed a clear, gradual rise in tumour size. This finding provided a reasonable radiographic basis for understanding the clinical progression, and the patient began receiving oral chemotherapy.

Every new MRI study should be compared with previous studies over as long a period as possible to detect the presence of gradual interval growth. The gradual growth of low-grade gliomas probably indicates that chemotherapy or radiotherapy should be considered in those patients whose symptoms adversely affect their quality of life.

In the case of anaplastic progression, a new focus of rapidly growing, contrast-enhancing tumour appears within an existing, non-enhancing mass. The interval to anaplastic progression is strongly age-dependent.¹³ Treatment of these patients is aggressive and involves irradiation and chemotherapy when progression is recognised.

Validity of imaging as a surrogate measure of tumour response to treatment

Patients with high-grade gliomas (ie, WHO grades III/IV and IV/IV) are routinely treated after surgery with a combination of irradiation and chemotherapy. In this instance, the neuro-oncologist is looking simultaneously for evidence of a tumour response to treatment and for tumour progression. The most relevant comparison images for the neuroradiologist and the clinician in this case are in most cases those from the most recent previous study.

Great effort has been put into clinical trials of new drugs for gliomas over the past 30 years. In the testing of new treatments for patients with gliomas, the standard three-phase design is used.¹⁶ The phase I and phase III study components, with their respective aims in identifying the maximum dose that can be tolerated and in comparing survival between patients receiving the new drug and controls, do not depend greatly on neuroimaging. However, this technique is an important tool in phase II studies, since the major goal is to find

evidence of effectiveness of the new drug as shown by radiographic response and clinical status.

Thus, whereas survival is the gold standard of efficacy for phase III studies, a surrogate measure of survival (eg, radiographic response rate) is used in phase II studies. Phase II studies are mostly done in patients with progressive tumours, and radiographic response rates are used because they can be measured more quickly than survival, and any survival measurement would be affected by previous treatment. The use of radiographic response as a surrogate endpoint for survival in phase II studies relies on the crucial assumption that radiographic response is a valid surrogate measure for a meaningful response as defined by survival.

As with systemic solid tumours, the categories of response are defined by imaging measurement rules that include complete response, partial response, stable disease, and progressive disease.¹⁷ Change in tumour size in most clinical trials is assessed simply by a measurement of two orthogonal diameters on the largest contrast-enhancing portion of the tumour taken from the same axial image on successive studies. The diameters are multiplied to give an estimate of tumour area.

Complete responses and partial responses are rare in clinical trials of patients with gliomas. Endpoints that measure the duration of stable disease, such as progression-free survival, are, therefore, more frequently used. A common endpoint for phase II clinical trials is progression-free survival after 6 months or 12 months. Phase II studies compare the proportion of patients free of progression for 6 months or 12 months with that of a historical control group. Progression-free survival is used because it is a more reliable endpoint than time-to-progression, in which the time to progressive disease is measured in all participants despite variation in the intervals between imaging studies in individual patients.¹⁸

Given the importance of imaging in the detection of antineoplastic-drug activity, we need to know whether radiographic response is a valid surrogate measure for overall survival. Studies have provided strong evidence that radiographic response predicts survival in anaplastic oligodendroglioma, for which response is associated with longer survival and with the loss of heterozygosity of chromosome 1p.¹⁹ For anaplastic astrocytomas, a study by the Radiation Therapy Oncology Group randomly assigned newly diagnosed patients to irradiation plus procarbazine, lomustine, and vincristine with or without bromodeoxyuridine.¹⁸ Patients with no disease progression at 6 months had median survival of 67 months compared with median survival of 19 months for patients who had shown disease progression by 6 months. Thus, for newly diagnosed anaplastic gliomas there is evidence that response (ie, duration of stable disease) is related to survival. However, we should emphasise that this was a study of adjuvant treatment, not salvage treatment, and most phase II trials are done in patients with progressive

disease. For the most common grade of glioma, glioblastoma multiforme, there is even less evidence that radiographic response is valid as a surrogate measure of overall survival in the phase II setting.²⁰ Thus, whether duration of stable disease is a valid measure of a survival-associated response remains unclear.

Difficulties in measuring tumour size in clinical trials

To complicate matters further, several features of glioma measurement make response assessment difficult. In the standard approach used in clinical trials, two orthogonal measurements are made of the gadolinium-enhancing portion of the tumour on the axial slice containing the largest lesion. That slice is measured on every imaging study in the series. However, the lesions tend to be irregular in shape; so the standard cross-sectional measurements do not truly estimate the size of the lesion. Many tumours have large areas of cystic

necrosis, which although included in the measurements are unlikely to respond to treatment. Disease progression commonly occurs within a small region of the tumour, so successive linear measurements across the same portion of the tumour from study to study might not detect evidence of early progression.

Thus, the use of a method based on cross-sectional diameter to measure the proportion of abnormal enhancement within the tumour could be a suboptimum approach for gauging response. A computer-aided volumetric analysis is better than the cross-sectional-diameter method, especially with respect to early detection of progression.^{21,22} Furthermore, the computer-aided volumetric approach shows substantially improved reliability within and between observers than the cross-sectional-diameter method. In the volumetric approach, a technician uses a computer program to draw a region of interest around a gadolinium-enhancing mass lesion on a single T1-weighted axial image. The computer then

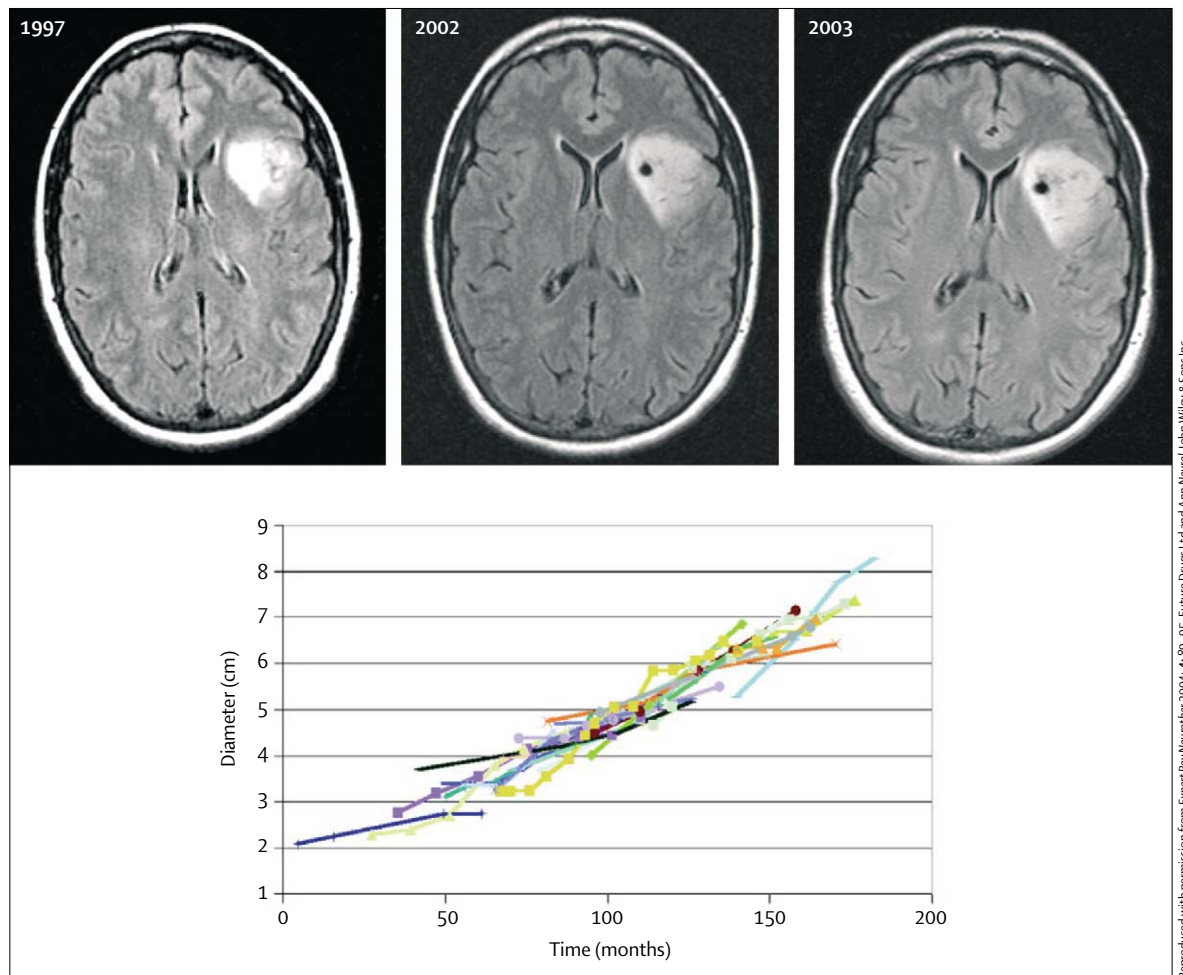


Figure 5: Patient with an oligoastrocytoma over 6 years of follow-up

Comparison of axial fluid-attenuated inversion recovery images, taken several years apart, showed interval enlargement of the tumour, whereas a comparison of the most recent previous examination and the new examination (an interval of several months) did not clearly show enlargement. Each line in the graph represents increasing diameter of a tumour over time.

draws a line along the margin between the enhancing and non-enhancing region on all adjacent images, using a pixel-intensity rule, and the program calculates enhancing, non-enhancing (eg, the centrally necrotic area), and total volumes (figure 6). However, validation of the advantage of this approach is scarce, especially in the setting of response assessment in phase II trials.

Heterogeneity in tumour imaging

Another relevant issue to be solved in the radiographic measurement of tumour activity during clinical trials relates to the intrinsic heterogeneity of gliomas. Gadolinium enhancement, tumour blood-volume measurements, and capillary permeability measurements all depend on angiogenesis and abnormalities of the tumour–blood barrier, whereas proton MR spectra and measurement of diffusion of water are affected by cell density and cell turnover as well as by sections of necrosis. As shown in figure 7, there can be a poor relation between tumour enhancement, cerebral blood volume, and metabolic changes on proton MR spectra. These findings suggest that the region of gadolinium enhancement presently measured in clinical trials does not represent the portion of the tumour that is most relevant in terms of response to treatment.

New techniques

Several exciting new approaches in brain-tumour imaging have become possible as a result of advances in MRI technology. Although the value of these techniques is still being defined, they find their place alongside routine anatomical imaging in both clinical trials and routine clinical care, particularly when a highly specific strategy for antitumour treatment, such as antiangiogenesis factors, is used.

Proton MR spectroscopy

Specific metabolic changes within tumour tissue can be identified with proton MR spectra in a semiquantitative

manner, providing additional information to routine anatomical imaging. Several changes in proton spectra are seen within high-grade glial tumours, whereas changes are much less evident or even absent in low-grade gliomas. Enhancement of the choline resonance, thought to be a consequence of amplified synthesis and turnover of membrane phospholipids, correlates with cell density in gliomas.²³ The choline resonance should be compared with the creatine resonance from contralateral healthy brain tissue for the most accurate quantification.²⁴ Potential uses of MR spectroscopy include refinement of preoperative differential diagnosis, biopsy-site selection, monitoring of response to treatment, and distinction of progressive tumours from treatment effects.

Studies have suggested that MR spectra obtained from brain tissue adjacent to the tumour can be valuable in distinguishing primary tumours from metastatic tumours.²⁵ In infiltrating primary tumours of the brain, higher than normal choline-to-creatine ratios are in sections adjacent to gadolinium enhancement, which contain tumour cells. In metastatic tumours, which have a discrete tumour–brain margin, choline resonance is typically not raised in brain tissue adjacent to the tumour. Thus, MR spectroscopy could be valuable in the refinement of preoperative diagnosis.

Proton MR spectra voxels with the highest concentrations of choline can be targeted for stereotactic-needle biopsy or for detailed regional histopathological review.²³ This approach can be particularly useful in patients in whom only stereotactic-needle biopsy, rather than resection, is possible. Notably, choline concentrations are generally higher in anaplastic astrocytomas than in glioblastoma multiforme, probably because necrotic tissue is included in the volume measured in glioblastoma multiforme.

Another possible role for proton MR spectroscopy is in the differential diagnosis of progressive, high-grade glioma and radiation necrosis.²⁶ However, this approach has proved difficult, mainly because a progressive tumour and radiation necrosis typically coexist. In studies, the average choline-to-creatine ratios are higher in the group with progressive tumours than in those patients with radiation necrosis, but the wide variation among individual patients in every group, makes practical application of inconsistent value. However, MR spectroscopy is useful in this setting when there is a greatly increased ratio of choline to contralateral creatine (>three to one) in an enlarging lesion, since this result suggests the mass consists mainly of active tumour. A choline-to-creatine ratio of less than two suggests predominance of radiation change. At intermediate values, proton MR spectroscopy is non-specific. Further work is needed to establish whether proton MR spectroscopy will be valuable in monitoring response to treatment.

Intrinsic limitations of proton MR spectroscopy at 1.5 T include the insufficient spectral resolution and

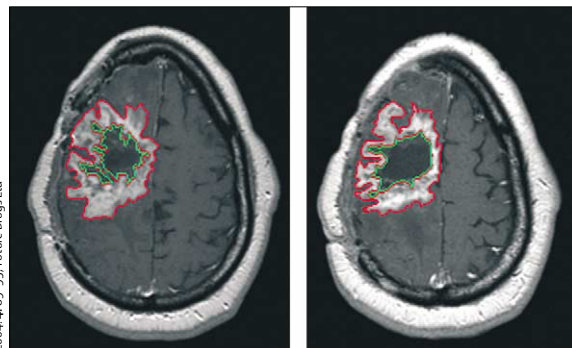


Figure 6: A computer-aided volumetric approach to measure an irregularly shaped glioblastoma. Shown here are two adjacent images of a glioblastoma. The glioblastoma contains a substantial region of central, non-enhancing, necrotic tumour. The computer generates a perimeter around the outer (red) and inner (green) enhancing margin of the tumour on successive axial slices by use of a pixel-intensity analysis.

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signal-to-noise ratio to measure additional specific metabolites of interest, poor spatial resolution with resultant volume averaging, and technical challenges involved in obtaining adequate spectra. Careful choice of the site of voxel placement is crucial, since several artefacts can degrade the signal. Voxels taken along the rim of peripheral enhancement show more informative spectra than those taken from a central necrotic region of a glioma. The heterogeneity of tumours calls for the use of spectroscopic imaging methods over the use of single-voxel MR spectroscopy.

Dynamic vascular imaging techniques

Dynamic MRI techniques can be used to measure important features of tumour vascularity *in vivo*, including the density and permeability of capillaries. Increased vessel numbers lead to higher regional cerebral blood volume, which can be measured relative to healthy brain tissue by perfusion MRI techniques. Thus, relative cerebral blood volume provides analysis of capillary density in gliomas. In adult astrocytomas, relative cerebral blood volumes correlate well with histopathological grade and survival.²⁷ A relative cerebral blood volume value of more than 1.5 is associated with the presence of high-grade tumour and with reduced survival in patients with diffuse astrocytomas. Low-grade oligodendrogliomas can have high relative cerebral blood volume without the same implications, owing to the heightened capillary density in all grades of this histopathological subset.

Capillary permeability can be established from the rate and amount of tumour-tissue enhancement after a bolus of gadolinium. Preliminary data show that permeability analysis is more sensitive and specific than blood-volume maps and routine gadolinium-enhanced MRI in identifying high-grade tumours and in distinguishing progressive tumours from radiation necrosis.²⁸

Diffusion imaging

Diffusion-weighted imaging is sensitive to the brownian movement of water molecules within and surrounding tumour cells.²⁹ This movement can be measured in many planes, and therefore provides not only a diffusion rate, but also a direction of movement (ie, a diffusion tensor). Diffusion-tensor imaging is valuable in differentiation of primary and metastatic tumours.³⁰ In the vasogenic oedema surrounding brain tumours there is greater than normal diffusion of water along compact white-matter tracts such as those found in the corpus callosum and the optic radiations. A lower rate of diffusion and more isotropic movement occur in the white matter surrounding primary tumours, presumably owing to the presence of the infiltrating tumour, than in vasogenic oedema surrounding a brain metastasis.³¹

Densely cellular tumours restrict the diffusion of water, whereas sections of necrosis or less densely

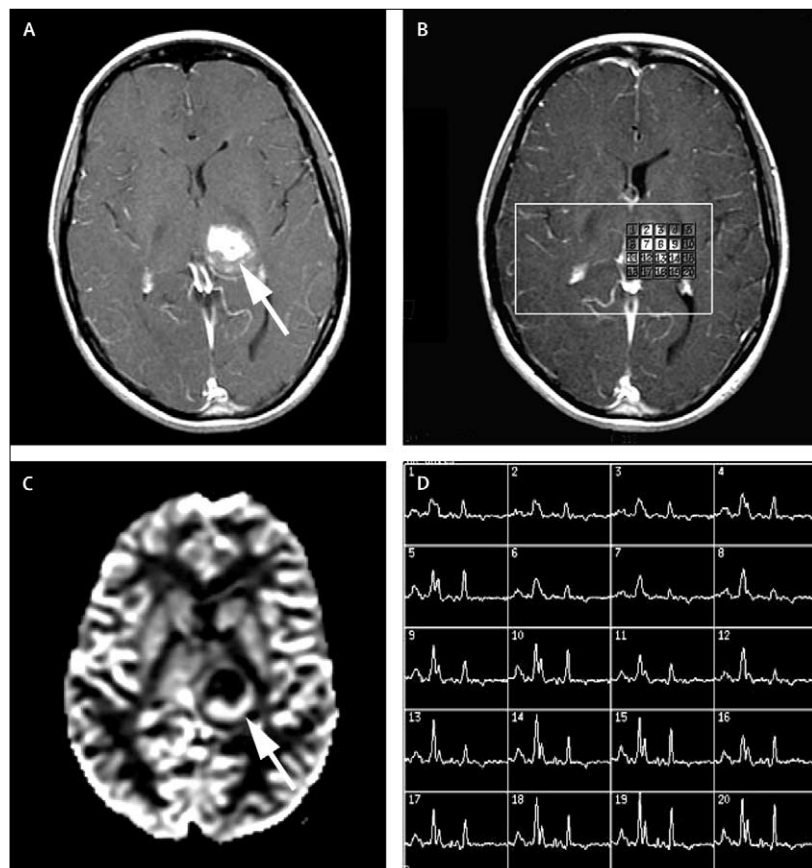


Figure 7: Heterogeneity in imaging features in glioblastoma multiforme

The white arrow indicates a minimally enhancing area (A). Greatly increased regional cerebral blood volume is shown in the minimally enhancing area (C). Multivoxel proton MR spectroscopy shows that the region of highest choline-to-creatine ratio also comes from the minimally enhancing portion of the tumour (B and D).

cellular tumours have raised water-diffusion rates. For this reason, the value of diffusion imaging in assessment of therapeutic response is under investigation.³² If tumours or sections within tumours with the highest cell density are more likely to respond to treatment, diffusion-weighted imaging might be able to predict response or provide a way to measure early response.

Diffusion-tensor imaging can also be used to provide maps of white-matter-fibre tracts (tractography) in brain tissue adjacent to tumours.³³ By elucidating the anatomical relation of motor and sensory pathway to tumour tissue, diffusion-tensor imaging has the potential to reduce surgical morbidity.

Functional imaging

Imaging dependent on blood oxygen concentration measures the effects of changes in the ratio of oxyhaemoglobin to deoxyhaemoglobin after dynamic metabolic changes in brain tissue associated with functional tasks, such as language and motor activity, and already has one well-accepted application in brain-

tumour imaging. These focal haemodynamic changes are displayed on an anatomical map with coregistered images of the brain tumour. This approach is already in widespread use as a preoperative mapping technique in an attempt to keep to a minimum intraoperative damage to eloquent brain areas.³⁴

Another potential application for this imaging method is in the assessment of the oxygen environment within brain tumours.³⁵ This technique would be particularly useful in clinical trials of approaches to raise oxygen concentrations within tumour tissue in an attempt to potentiate DNA damage from radiation or chemotherapy.³⁶

Intraoperative MRI

During the past 10 years, MRI has been introduced into neurosurgical operating rooms to allow real-time imaging during surgery.³⁷ Intraoperative MRI has several potential advantages. From the standpoint of tumour diagnosis, it can be used to guide the surgeon more accurately to small lesions, thus, limiting the extent of craniotomy and improving the chance of obtaining diagnostic tissue. Compared with routine stereotactic procedures, this approach is not restricted by tissue movement during craniotomy.

Studies³⁸ have shown improvement in the extent of tumour resection with the use of intraoperative MRI, but improved survival has not yet been shown. Real-time visualisation of the resection margin would also probably make these more thorough resections safer, and improve surveillance for intraoperative complications. Increasing the extent of resection in patients with low-grade gliomas has provided the strongest rationale for intraoperative MRI.³⁷

Intraoperative MRI systems are available with either low (0.2 T) or high (1.5 T) field strength. High-field-strength systems carry the potential of better imaging quality and the opportunity of advanced imaging features such as diffusion, angiography, and spectroscopy. However, the size and cost of the high-field-strength magnets are pronounced disadvantages.³⁹

Intraoperative imaging has some limitations. Titanium neurosurgical instruments are needed, and the high magnetic-field strength of these devices poses a potential risk from ferrous substances in the operating room. There might be compromises in the positioning of the patient, access by the surgeon, and sterility. Image-acquisition time is only about 2 min for each sequence, but the need to move the patient in and out of the scanner lengthens the operation time.³⁹ The interpretation of images obtained during surgery can be challenging because, in addition to the structures seen on preoperative films, intraoperative images can show surgical artefacts from air or blood. Finally, a barrier to widespread implementation of these techniques has been the substantial expense and maintenance of the scanning equipment.

Molecular imaging

This is a rapidly emerging sphere of investigation that seeks to achieve imaging of molecular processes within brain-tumour cells *in vivo*.⁴⁰ In one example of the use of MRI to image smart probes, tumour-cell-specific uptake of monocrystalline iron oxide nanoparticles can be achieved owing to the high concentration of transferrin receptors on the cells. Thus, these tumour cells have a high rate of endocytosis of the nanoparticles, and they can be imaged with MRI. In another example that has been tested in experimental models, cells can be induced to overexpress transferrin receptors, and these cells can then be selectively detected *in vivo* by MRI after administration of monocrystalline iron oxide nanoparticles.

Paramagnetic chelates that can change their magnetic properties on enzymatic hydrolysis are under investigation. For instance, a gadolinium galactopyranose substrate shows greater relaxivity after β -galactosidase-mediated hydrolysis. Thus, the presence of ectopically-expressed β -galactosidase can be indirectly detected by MRI. Magnetic nanosensors are being developed that might be able to detect specific DNA or RNA sequences. Enzymes, such as tyrosinase that have a high metal-binding capacity, might also be imaged with MRI when overexpressed.

Potential future development of functional and metabolic imaging techniques

Functional and metabolic imaging techniques will continue to progress rapidly. Important approaches to tumour imaging will include capillary permeability mapping, phosphorus MR spectroscopy, real-time intraoperative spectroscopic measurements, and molecular imaging. Techniques will progress to assess the specific feature of the tumour that is being targeted by new therapies, as is happening now with treatments directed at tumour vascularity. There will be at least two major challenges for these new techniques. First, rigorous, quantitative analysis of the validity of every imaging approach will be crucial. Second, inherent biological variability between and within tumours will probably pose a formidable barrier to the application of functional and metabolic imaging techniques. These techniques should help to identify more rapidly better therapeutic drugs for patients with these devastating tumours.

Search strategy and selection criteria

Publications for this review were identified by use of the PubMed and references cited in relevant articles. "Brain neoplasms", "magnetic resonance imaging", and other search terms were used to find articles on brain-tumour imaging. Only articles published in English were used.

Conflict of Interest

We declare no conflicts of interest.

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