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## Neurosurgical Management of Gliomas

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### 1. Introduction

Gliomas are the commonest brain tumours. They are tumours derived from the three most common glial cells, the astrocytes, oligodendrocytes and ependymal cells, with each cell type giving rise to its named tumour i.e. astrocytoma, oligodendroglioma and ependymoma. Other less abundant glial cells give rise to rarer tumours e.g. subependymal astrocytes leading to subependymoma. Table 1 summarises the different gliomas, their incidences and subtypes (Bigner et al, 1996; Han et al, 2010, Kozak & Moody, 2009; Louis et al, 2007). The grading depends on the number of histological features of malignancy such as cellular atypia, presence of mitoses, endothelial proliferation, and necrosis and is known as the World Health Organisation grade (WHO). For the astrocytomas, grade I has none, grade II has one feature, grade III (anaplastic astrocytoma) has two and grade IV (glioblastoma) has three or four. The majority of gliomas arise in the brain, with only a minority in the spinal cord.

Surgery for brain tumours is very different from surgery for peripheral tumours. The major difference is that brain tumours directly affect mental function. The effect on quality of life is therefore more pronounced than a peripheral tumour causing a physical disability in isolation. Unlike other major cancers such as breast, lung and colon where large advances have been made over the last twenty years (Office for National Statistics, 2010), little advance has been made with brain tumours. As a result, the mortality of patients with glioblastoma (grade IV astrocytoma) has not improved much over this period (Cancer Research UK, 2010; Erridge et al, 2011).

In this chapter we will consider surgery for gliomas. Surgery has a role to play in virtually all gliomas at some stage or another. The extent of surgery varies from a simple biopsy, to establish diagnosis, to a more radical attempt at complete removal. Although some surgical principles universally apply, in many cases management varies from country and country, and even from centre to centre e.g. treatment of an elderly person with glioblastoma may vary from palliative care with no treatment, to maximal debulking followed by radiotherapy and chemotherapy. Some of these decisions on how aggressive one should treat the patient depend not only on surgical accessibility of the lesion but also on family views, cultural values and of course cost and availability of resources for neurosurgery. Such life-death decisions are part of the daily routine of neurosurgical practice.

Prolonging life may be less important than maximising quality of life. Sometimes the two go hand in hand, however in other circumstances, the extra time gained by surgery may result in a life of misery spent in hospital feeling sick on drugs with questionable benefit.

Glial cell	Sub-category	WHO Grade	Variants	Epidemiology
Astrocyte	Pilocytic	1		M : F, 1.2:1 0.3/100,000
	Diffusely infiltrating	2	Protoplasmic Gemistocytic Fibrillary	M : F, 1:1 0.2/100,000
		3 (anaplastic)		M : F, 1.4:1 0.5/100,000
		4 (glioblastoma multiforme)	Giant cell Gliosarcoma	M : F, 1.6:1 2.6/100,000 1-2.5% GBM 1.8-2.5% GBM
	Rarer types			
	Subependymal giant cell astrocytoma	1		M > F 0.51% gliomas,
	Pleomorphic xanthoastrocytoma	1		M = F Rare
	Desmoplastic cerebral astrocytoma of infancy	1		1 <sup>st</sup> 18/12 life Rare
Oligodendrocyte	Oligodendroglioma	2		M : F, 1.3:1 0.3/100,000
	Anaplastic oligodendroglioma	3		M : F, 1.5:1 0.1/100,000
Mixed	Oligoastrocytoma	2		M : F, 1.9:1 0.1/100,000
	Anaplastic oligoastrocytoma	3		
	Other mixed			
Ependymal cell	Ependymoma	2	Cellular, papillary, clear cell, tancytic	M : F, 1.3:1 0.2/100,000
	Anaplastic ependymoma	3		
	Myxopapillary ependymoma	1		M : F, 1.6:1 0.0/100,000
	Subependymoma	1		

Table 1. Classification of gliomas, grade and incidence

## 2. Preoperative management

In the United Kingdom, most patients present through Accident and Emergency. There are three main ways they present: with a focal neurological deficit; seizures; or with high

intracranial pressure (this is often progressive, but may be sudden onset if the tumour bleeds into itself). These presenting symptoms and signs lead to CT/MR as an emergency, followed by referral to a neurosurgery unit. If brain oedema is evident on imaging, steroids are started.

## 2.1 Medications

Dexamethasone is preferred due to its low mineralocorticoid activity (hence little sodium and water retention). The mechanism of action of steroids remains unclear. Dexamethasone was introduced in 1960s following Gailicich's seminal paper on its use of alleviating oedema in brain tumours, and it revolutionised the outcome of surgery for brain tumours (Gailicich et al, 1961a, 1961b). The standard dose is 4mg four times a day given orally or intravenously, following a loading dose of 10mg, and an improvement in symptoms is often seen within a few hours (Kesari et al, 2002). If a patient has had a seizure due to their tumour, an antiepileptic should be given. Phenytoin is the preferred agent in the acute setting, although Carbamazepine may be better for focal seizures. Phenytoin elimination is via zero-order kinetics near the therapeutic level and approximately 90% is protein bound. A loading dose is required (18mg/kg intravenously), which must be given slowly to reduce risk of hypotension and arrhythmias (Meek et al, 1999). The daily dosage is usually 300mg once a day, and serum levels should be measured daily until a satisfactory level is achieved. The advantages of phenytoin are the fast acting nature and cheap cost. Disadvantages include potentially reduced cognitive function, hypersensitivity, megaloblastic anaemia and cerebellar degeneration. Phenytoin is teratogenic. Toxicity (which may develop at concentrations above 20µm/ml, but more commonly above 30µm/ml) manifests with cerebellar signs, confusion and CNS depression. Carbamazepine has a half-life of 20-55 hours. A low dose should be commenced and incremented slowly, with regular checks of haematological function due to its potential for marrow suppressive effects. Its main advantages are the low risk of cognitive and dysmorphic side effects. The main disadvantages are the unavailability of parenteral form and its metabolic autoinduction (Tudur Smith et al, 2002). We will not describe the various antiepileptics here and their advantages and disadvantages in detail.

## 2.2 Multidisciplinary team

In most centres, tumours are discussed in a neuro-oncology multi-disciplinary meeting (MDT) to determine the best way to proceed with treatment. If patients present as an emergency however, their surgical treatment should not be delayed by the MDT. If not an immediate emergency, patients with a new diagnosis of glioma can be managed in either the inpatient or outpatient setting. A more aggressive approach would be to admit the patient directly to the neurosurgical unit from the emergency department or the referring hospital, and to plan for surgery on that admission over the following days. A less aggressive approach would be to see the patient in the outpatient clinic, especially when a "watch and wait" policy is a reasonable option. It is important to note the patient should not wait too long to be seen in this setting. Often, little or no information is given to the patient from the referring doctors, causing significant anxiety.

## 2.3 Conventional imaging

The practice of imaging of brain tumours has evolved over the past 20 years from a strictly morphology-based discipline to one that encompasses function, physiology as well as

anatomy. Imaging not only allows determination of the location and extent of tumour but also has a key role in primary diagnosis, biopsy target selection, guiding resection margins, radiotherapy planning and delineating of tumour from functionally important neural tissue. Following treatment, imaging is used to quantify treatment response and extent of residual tumour. At follow-up or in the pre-op monitoring of inoperable low-grade glioma, imaging helps to determine tumour progression and to differentiate recurrent tumour growth from treatment-induced tissue changes, such as radiation necrosis.

In the majority of cases, plain computed tomography (CT) scans are the first brain imaging studies performed when investigating patients with suspected brain tumour. This is because CT is widely available, fast, relatively risk-free, and well tolerated. It has the advantage of being sensitive in detecting acute haemorrhage, hydrocephalus and mass effect. If an abnormality is detected on plain CT then intravenous contrast is administered which allows assessment of blood brain barrier (BBB) integrity and delineation of contrast enhancing tumour border, if present. Due to its intrinsically low soft tissue contrast, CT is not optimally suited for detecting subtle changes in brain parenchyma or patterns of tumour infiltration (Ricci, 1999), even with the addition of intravenous contrast agent. CT is inferior to MRI in its soft tissue resolution, multi-planar capability and physiology-based applications. Finally, CT involves ionizing radiation and its iodinated contrast agent can cause allergic reaction (Cha, 2009).

Magnetic resonance imaging has become the standard of imaging patients with brain tumours (Jenkinson, 2007). MR techniques can be broadly classified into 'conventional' and 'advanced'. Conventional MRI provides qualitative images of normal anatomy and pathology, whilst advanced MR techniques allow quantitative and semi-quantitative measurement of cerebral blood flow, water movement and the chemical composition of the tissue under interrogation. It is these non-invasive methods of assessing tumour physiology that are becoming increasingly important in neuro-oncology decision making. In this section we will firstly introduce the characteristic glial tumour appearances on conventional MRI studies then discuss advanced imaging modalities, focusing on diffusion MR and its potential role in tumour diagnosis, delineation and treatment planning.

### **2.3.1 Pilocytic astrocytomas (PA), grade I**

PA are slow growing, well circumscribed tumours. Their characteristic imaging appearance is of a cystic cerebellar mass with an enhancing mural nodule. They are located in the cerebellum in 60% of cases and optic nerve/chiasm in 30% (also adjacent to the third ventricle and brainstem). On plain CT, PA form discrete cystic or solid masses with little or no surrounding oedema. They contain calcium in 20% of cases, rarely haemorrhage and frequently present with obstructive hydrocephalus. Over 95% of PA enhance, but enhancement does not indicate malignancy. On T2 weighted and FLAIR MRI scans the solid portion is hyperintense to gray matter. Cystic portions are hyperintense to CSF. On T1 studies, the solid portion is iso/hypointense to grey matter and there is intense heterogeneous enhancement of the solid portion. The cyst wall occasionally enhances.

### **2.3.2 Diffuse astrocytoma (DA), grade II**

Diffuse astrocytomas are typically focal or diffuse non-enhancing white matter lesions. Two thirds of DA are located in the cerebral hemispheres (of which 1/3 in the frontal lobe, 1/3 temporal lobe) and one third are located infratentorially (50% of brainstem gliomas are low

grade astrocytomas). DA are tumours of the white matter with only 20% involving deep grey matter structures (thalamus or basal ganglia). They may be variable in size and are typically homogeneous lesions causing local cortical expansion and distortion of surrounding structures. Although they may appear to have a circumscribed edge on imaging studies, studies have revealed viable tumour cells are found beyond the image margin. Plain CT studies of DA reveal ill-defined hypo or iso dense lesions. Calcification is seen in 20% of cases and rarely intra-tumoural cysts. They do not typically enhance following the administration of contrast and the presence of enhancement is likely to indicate focal anaplastic transformation. Conventional MRI studies of DA (figure 1) identify homogeneous, lesions which expand white matter and adjacent cortex. They are typically hypointense on T1 weighted MR and hyperintense on T2 weighted and fluid attenuated inversion recovery (FLAIR) studies.

### **2.3.3 Oligodendroglioma (ODG), grade II**

ODG is a well-differentiated, diffusely infiltrating tumour which typically involves subcortical white matter and cortex. 85% of ODG are supratentorially located and are most commonly seen in the frontal lobe however may also be present in temporal, parietal and occipital lobes, posterior fossa and within the ventricle (1-10%). They may be variable size and are most commonly of mixed density of plain CT with calcification seen in 70-90% of cases and cystic degeneration in 20%. Approximately 50% enhance following contrast administration on both CT and MRI. On T1-weighted MRI studies ODG are heterogeneous and hypo or isointense to grey matter. They are cortical and subcortically located and cause surrounding cortical expansion. They are hyperintense on T2/FLAIR. Anaplastic oligodendroglioma (AO), have similar appearances as ODG however will contain foci of malignant progression which may be seen as new contrast enhancement, necrosis, cystic change or haemorrhage.

### **2.3.4 Anaplastic astrocytoma (AA), grade III**

In common with DA, anaplastic astrocytomas are infiltrating lesions predominantly involving white matter. AA are more commonly within the cerebral hemispheres (especially temporal lobes), they may be of variable size and may appear well-circumscribed however, as in DA, tumour cells are almost always found beyond the tumour border on imaging. On CT studies, AA are low density, ill-defined mass. They rarely contain calcification and the majority do not enhance (those that do display patchy foci of enhancement). On T1 weighted MR imaging they are mixed isointense to hypointense white matter lesions. They are heterogeneously hyperintense on T2 weighted and FLAIR MR. Evidence of ring enhancement, prominent flow voids and cysts may suggest progression of AA to more malignant forms.

### **2.3.5 Glioblastoma multiforme (GBM), grade IV**

GBM are most commonly located in supratentorial white matter within the frontal, temporal and parietal lobes however may infiltrate across white matter pathways to involve contralateral cerebral hemisphere. They may be of variable size and morphology. Most frequently they are poorly marginated, diffusely infiltrating necrotic lesions, which in rare cases are multifocal or multicentric. GBM appear as irregular, isodense or hypodense lesions with central necrotic hypodensity on plain CT. They frequently exert significant local mass effect and have peri-tumoural oedema and tumour infiltration. Of all glial tumours, GBM

are the most likely to contain haemorrhage. Conventional MRI of GBM (figure 2), reveal irregular iso or hypo intense masses on T1 weighted studies and heterogeneous hyperintense masses with adjacent oedema/tumour infiltration on T2 weighted/FLAIR MRI. GBM frequently contain a necrotic core, tumoural cysts, focal haemorrhage, and flow voids secondary to tumour neovascularity. GBM most commonly have thick irregular enhancing margins surrounding central necrosis however may exhibit solid, ring or patchy enhancement on gadolinium enhanced T1 weighted MRI.

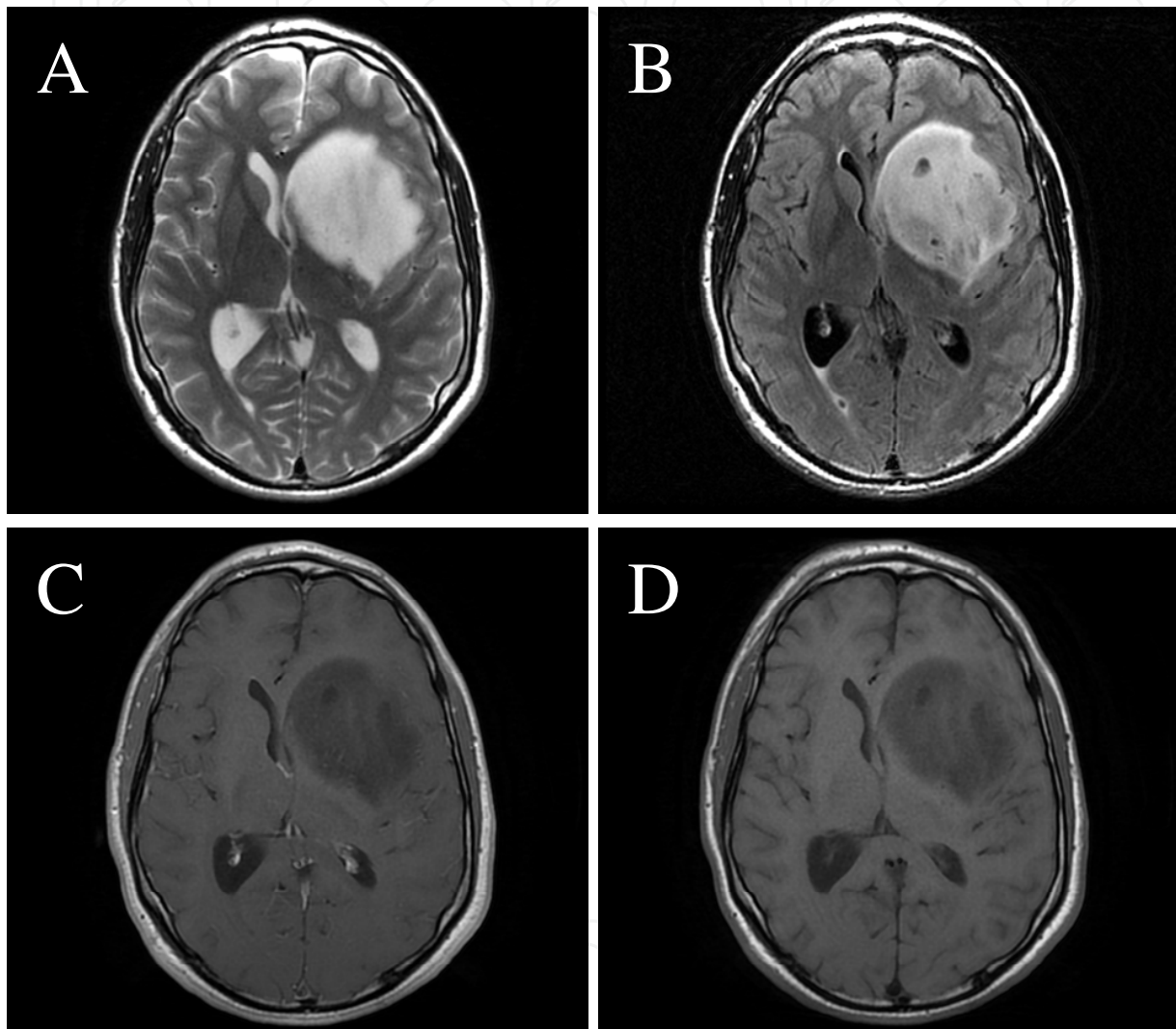


Fig. 1. MRI images of left fronto-temporal diffuse astrocytoma. A. T2-weighted image, B. Fluid attenuated inversion recovery (FLAIR) image, C. T1-weighted image following administration of 0.1 mmol/kg gadoterate meglumine, Dotarem®), D. T1-weighted image.

### 2.3.6 Ependymoma grade II or III

Ependymoma are slow growing tumours of ependymal cells, of which, 2 / 3 are infratentorially located (typically within the IVth ventricle) and 1 / 3 supratentorial (within periventricular white matter). They are of irregular shape, typically modelling to the shape of the ventricle or cistern. 50% of ependymomas calcify and they are heterogeneous lesions (iso or hypo intense on T1 and T2 MRI) and display irregular degrees of enhancement.

### 2.3.7 Rare gliomas

**Gliosarcoma (grade IV).** Gliosarcomas are rare malignant neoplasms containing both glial and mesenchymal elements. Although their imaging appearances are often indistinguishable from GBM, they more commonly exhibit dural invasion and involvement of surrounding skull. In common with GBM, they infiltrate white matter and are typically supratentorially located however may have a discrete portion. They are heterogeneous masses with thick irregular enhancement on CT and share the features of GBM on conventional MRI, as a result gliosarcoma are frequently only identified following formal tumour histological analysis.

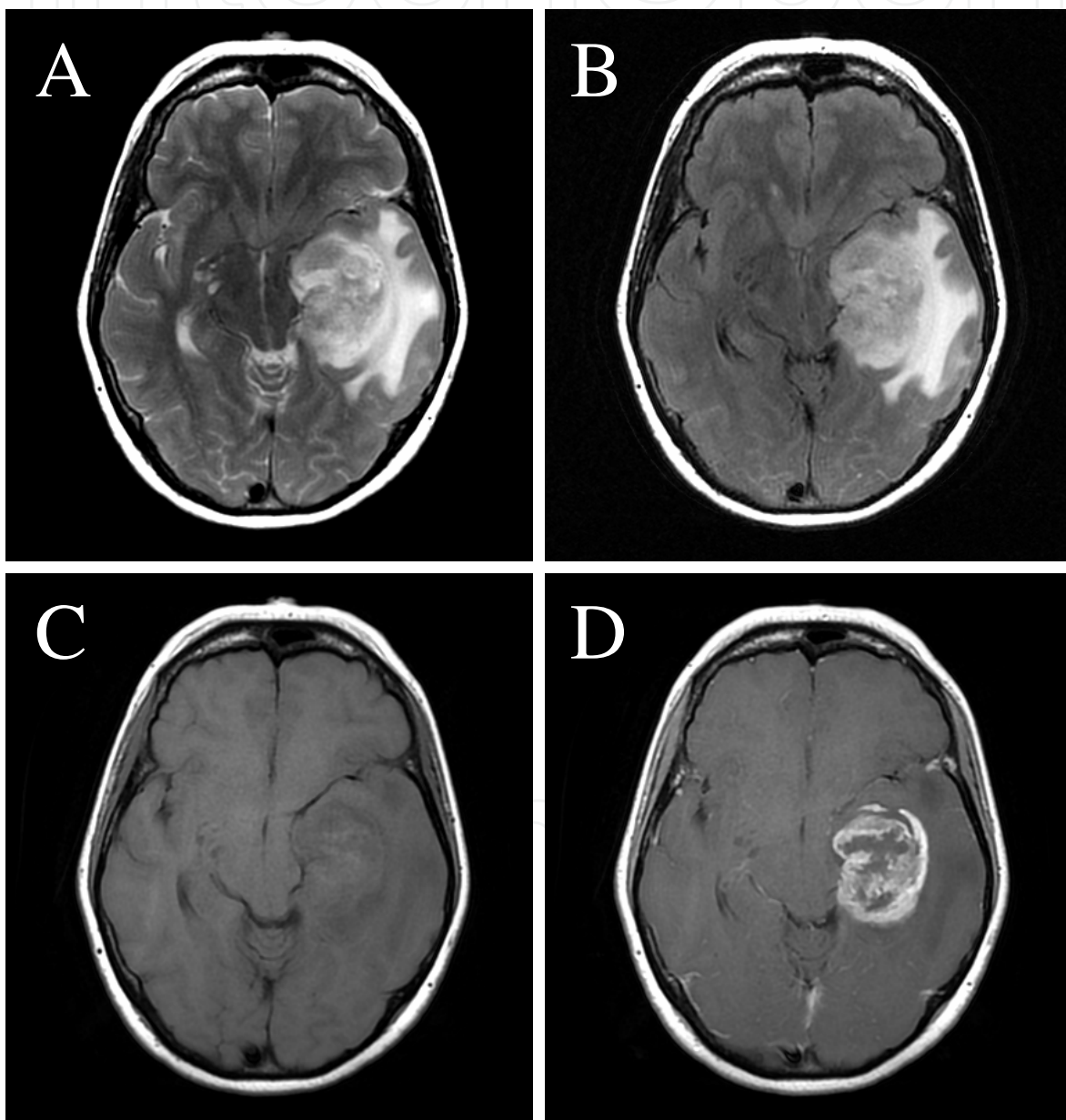


Fig. 2. MRI images of left temporal glioblastoma. A. T2-weighted image, B. Fluid attenuated inversion recovery (FLAIR) image, C. T1-weighted image, D. T1-weighted image following administration of 0.1 mmol/kg gadoterate meglumine, Dotarem®)



**Gliomatosis cerebri (grade IV).** Gliomatosis cerebri (GC), are diffusely infiltrating glioblastoma lesions involving two or more lobes of the brain and are frequently bilateral. Although they are typically hemispheric they may involve cortex in 19% of cases and as well as diffuse white matter may involve basal ganglia/thalami (75%), corpus callosum (50%), brainstem/spinal cord (10-15%) and cerebellum (10%). GC are infiltrative in nature, yet may preserve underlying brain architecture and cross the midline via corpus callosum or massa intermedia. GC may exhibit subtle asymmetric loss of grey-white differentiation and mild mass effect on plain CT and do not typically enhance (focal enhancement may indicate malignant progression or a focus of anaplastic change). They are iso or hypo intense on T1 weighted MR and homogeneously hyperintense on T2-weighted/FLAIR MRI.

**Pleomorphic xanthoastrocytoma (PXA), grade II.** PXA are a distinct type of benign, supratentorial (98% of cases), astrocytoma affecting young adults. Their characteristic feature is of a cortical mass with adjacent enhancing dural 'tail' with an associated tumour cyst (50-60% of cases) and mural nodule. They are most commonly seen in the temporal lobe and may be of variable size. Despite their circumscribed appearance they often infiltrate into brain. On CT, PXAs are hypodense with a mixed density nodule, they have minimal surrounding oedema and typically avidly enhance. On T1 weighted MRI, they are hypo or isointense to surrounding grey matter and enhance following administration of gadolinium. The solid portion is hyperintense or of mixed signal intensity on T2-weight or FLAIR studies. Any cystic portions are isointense to CSF.

## 2.4 Advanced imaging

Despite its superb soft tissue contrast, multi-planar capability and non-invasive nature, conventional MRI is largely limited to depicting morphological abnormalities. Different disease processes can appear similar on anatomic imaging, and conversely a disease entity may have varied imaging findings. The underlying metabolic or functional integrity of brain cannot be adequately evaluated on anatomical MRI alone. To that end, several physiology-based MRI methods have been developed to improve tumour characterisation including spectroscopy, radionuclide imaging (PET and SPECT), dynamic susceptibility contrast MRI, blood oxygen level dependent (BOLD) MRI and diffusion imaging.

### 2.4.1 Magnetic resonance spectroscopy (MRS)

Proton MRS can be used to non-invasively evaluate the biochemical structure of tumour tissue and has been used as an adjunct to conventional MRI to diagnose 'likely' tumour grade prior to surgery, guide stereotactic biopsy, plan radiotherapy margins and differentiate radiation necrosis from tumour recurrence. Spectroscopy signals are either localised from a single selected voxel or from multiple voxels (also known as chemical shift imaging). Proton spectra reveal varying peaks at defined resonant frequencies. The commonest peaks studied in brain tumours are:

- i. N-acetyl aspartate (NAA): reduced in disorders resulting in axonal loss therefore considered a surrogate marker of integrity of the neurone.
- ii. Choline (cho): choline compounds involved in breakdown and manufacture of cellular membranes. Choline increases with membrane turnover.
- iii. Creatine (Cr): involved in energy metabolism (ATP synthesis)
- iv. Lipid: not normally seen in brain. Their presence indicates membrane breakdown and necrosis.

v. Lactate: levels increase in situations of anaerobic glycolysis

Glial tumours have a reduced NAA/Cr ratio and spectroscopic profiles such as high lactate and lipids are indicative of malignant tumour. Tumour cell density may be reflected by the magnitude of choline peak and choline:NAA ratio. MRS is useful in distinguishing neoplastic from non-neoplastic lesions however owing to the lack of reproducible 'metabolite profiles' of glial tumour subtypes, its role in routine diagnosis has yet to be elucidated.

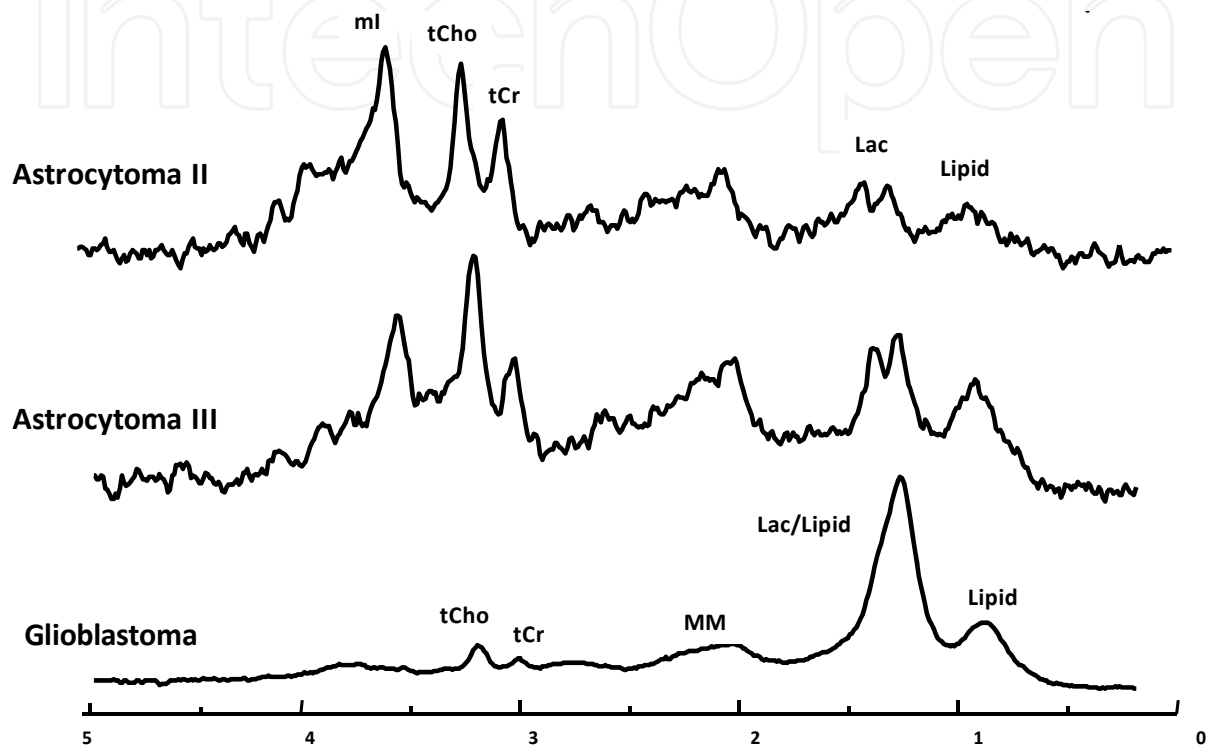


Fig. 3. Characteristic spectroscopic profiles of glial tumours. Choline (tCho) is considered a marker of tumour cell membrane proliferation and is seen to increase with tumour grade. Similarly an inverse relationship between NAA/Cr and Cho/Cr ratio and tumour grade may be used to differentiate high grade from low grade glioma. Higher lipid levels are seen in GBM, presumably a result of necrosis. Higher lactate levels with higher grades.

#### 2.4.2 Diffusion imaging

The development of MR pulse sequences sensitised to the movement of water molecules has enabled visualisation and mathematical characterisation of the magnitude and direction of water diffusion within the brain. Diffusion weighted imaging was introduced into routine practice in the 1990s, and generation of maps of apparent diffusion coefficient (ADC) have been used to differentiate cystic lesions (arachnoid from epidermoid cysts) and abscess from tumour. Numerous studies have been performed to characterise the glial tumour environment using ADC values which are affected by both the extent of local vasogenic oedema and the degree of tumour cellularity. Despite several studies confirming a correlation between cellularity and ADC, a tumour-specific DWI profile has not been identified. The underlying assumption of DWI is that water diffusion occurs in all directions (i.e. is isotropic). Investigators proposed that diffusion is likely to be restricted and directional (anisotropic) due to the influence of local intra and extra cellular structures such

as white matter fibres and myelin sheaths. Mathematical determination of the resultant diffusion ellipsoid requires the use of a tensor, which contains information about the magnitude and principal directionality of diffusion on a voxel scale. This information has enabled calculation of rotationally invariant indices such as mean diffusivity (MD) and fractional anisotropy (FA) as measures of isotropic and anisotropic diffusion respectively. These metrics have been applied to a range of intracranial pathology and studies have revealed relationships between FA and tumour cell density and have attempted to characterise the peri-tumoural oedema of low and high-grade glioma yet this has yet to be used routinely in clinical practice. The most promising role for diffusion tensor imaging in glial surgery is its application in tractography. Use of this technique has allowed:

- i. Definition of the anatomical relationship of a tumour to local white matter pathways, which may be incorporated on to image guidance systems to guide the surgical approach intra-operatively.
  - ii. Evaluation of whether there is displacement, invasion or destruction of surrounding white matter tracts by tumour.
  - iii. Knowledge of location of white matter tracts may assist intraoperative fibre stimulation and guide extent of resection
  - iv. Evidence of intact pathways following surgery may predict motor deficits and recovery.
- Although the strong similarity between generated white matter structures using DTI tractography and post mortem anatomical dissection, the technique is unable to accurately define the anatomy of individual axons and may be complicated by crossing fibres thus, at present, its role is primarily for macroscopic delineation of tract configuration.

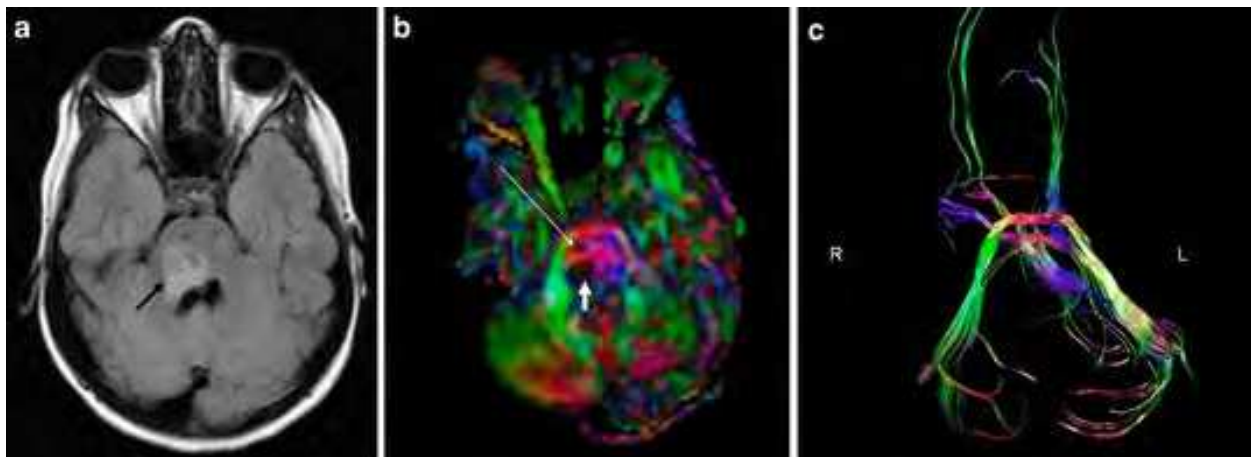


Fig. 4. A 6-year-old child with tumor arising from the brainstem. *a* Axial FLAIR image shows a tumor within the right middle cerebellar peduncle (*arrow*). *b* Axial color map shows loss of anisotropy within the right medial lemniscus resulting in lack of blue (*short arrow*). The right corticospinal tract (*long arrow*) is attenuated and has diminished anisotropy. *c* Coronal image derived from tractography shows leftward displacement of the right corticospinal tract (Rollins, 2007).

### 3. Common brain gliomas – surgical management

#### 3.1 Glioblastoma multiforme (grade IV)/ anaplastic astrocytoma (grade III)

Grade III and grade IV astrocytomas are also called high-grade tumours. If the patient is young and the tumour “resectable,” the primary aim is to remove as much as possible. The greater the extent of tumour removed, the better the time to tumour progression and

survival (Keles et al, 1999). Surgery not only prolongs life, but also improves quality of life and the effectiveness of adjuvant therapy (Abrudan et al, 2011, Kiwit et al, 1996; Ryken et al, 2008). When considering surgery, three of the most important prognostic factors for surgeons are the patient age, the tumour grade and the patient's performance status (Karnofsky score) at presentation (Buckner, 2003; Wu et al, 2010). Each is an independent factor for survival; favouring survival is younger patient age, Karnofsky score  $\geq 70$  (meaning independence) and lower tumour grade. Tumour resectability predominantly refers to the tumour location and the ability to remove the tumour without leaving the patient dead or moribund. Superficial, non-eloquent lesions (e.g. non dominant frontal) are considered highly resectable. Non-resectable lesions include deep, eloquent brain e.g. brainstem gliomas. Another subset that fall under the non-resectable lesions are butterfly gliomas, so called due to their characteristic radiological appearances based around the corpus callosum, extending bifrontally. These often occur in elderly patients and treatment is usually biopsy alone. Prognosis is dismal (Agrawal, 2009).

Surgery is simple in most cases, the aim is to remove as much tumour as possible without causing damage to brain. A craniotomy is performed at the required location, followed by debulking of the tumour with suction and/ or Cavitron Ultrasonic Surgical Aspirator (CUSA). Suction pulls on surrounding brain tissue, CUSA advantageously does not. High-grade tumours are highly vascular, and may bleed substantially during surgery. It is common to encounter necrosis and thrombosed vessels intraoperatively. This is surgical evidence of a high-grade lesion. With substantial bleeding, it is important to continue resecting, as once the tumour and associated abnormal blood vessels are removed, the bleeding will stop. Do not fall into the trap of stopping every few seconds to assess and coagulate as this will take too long, will increase blood loss and will probably result in less tumour removed. The tumour often feels tougher than brain, and any cystic components have a characteristic straw coloured fluid. Surgical judgement (from feel and experience) is required to know when to stop resecting. These are diffuse tumours and therefore there is no clear margin. There is a continuum from what is all tumour to more and more percentage of brain mixed with tumour, and when to stop depends also on the eloquence of adjacent brain. At the end of the operation, haemostasis is imperative. This is achieved with a combination of coagulation, Surgicel, and woolly balls. Surgicel and woolly balls will only stop venous bleeding. We always ask the anaesthetist to increase the patient's blood pressure to normal before closing. Any arteries in spasm will then begin to bleed. It is obviously important to know this before closing, so that we coagulate rather than ignore any unaddressed bleeding to avoid postoperative haematoma! Once we are satisfied the operative field is dry, we close up and the operation is finished (Schmidek, 2005; Slacman M, 1996).

Some centres operate on high-grade tumours awake. The patient is anaesthetised for the skin incision and craniotomy parts. The patient is woken once the brain and tumour is exposed. This allows the surgeon to maximise tumour resection without causing a disabling neurological deficit. Awake surgery is not widely accepted for GBM and anaplastic astrocytoma due to their aggressive and infiltrative nature. Although there is well-documented evidence of a significant difference in outlook between a small biopsy vs. extensive resection (Arudan et al, 2011; Keles et al, 1999; Ryken et al, 2008) there is probably little to be gained in outlook between extensive resection versus achieving another small percentage resection with awake surgery.

Recently, some surgeons advocated the intraoperative use of fluorescent dye, 5-aminolevulinic acid (5-ALA), although currently this is not widely used. 5-ALA is a natural biochemical precursor of haemoglobin, which results in accumulation of porphyrins within malignant glioma tissue. Its selective intratumoural synthesis enables an accurate delineation of the tumour boundary, seen via a modified neuromicroscope. 5-ALA has been shown to improve gross total resection defined by early post operative MRI, as well as improve 6 month progression free survival (Stummer et al, 2006).

Neuronavigation (e.g. Stealth, see figure 5) is another aid to glioma surgery. This utilises preoperative CT and/or MRI images to map the patient's anatomy in a 3-dimensional configuration, calibrated using specific landmarks on the patient. It can be used to map the bone flap and to guide debulking of the abnormal tissue. The main disadvantage of this widely used technique is that the brain moves once the skull and meninges are opened, thus diminishing the accuracy of the neuronavigation (Warnick & Bath, 2002). Newer techniques include the use of intraoperative ultrasound. This allows for an updated picture on each application of the ultrasound wand, and therefore corrects for any intraoperative brain shift with almost realtime information on the tumour location and extent. The financial cost of this is high.

If a tumour is deemed unresectable but there has been an agreement to give adjuvant treatment, a biopsy is required for histological confirmation of grade. This can be performed either Stealth or stereotactic guided. The former is frameless, the latter is a frame guided system. Both yield a similar diagnostic accuracy with similar complication rates (Doward et al, 2002). Grade III glioma treatment is the same as for grade IV, including maximal resection if possible followed by radiotherapy and temozolomide. PCV chemotherapy (procarbazine, lomustine and vincristine) is used as a second line (Theeler & Groves, 2011).

### 3.1.1 Other considerations in high grade gliomas

**Gliadel wafers.** These are made by MGI pharma, Inc and contain polifeprosan 20 with carmustine implant, an alkylating agent used for brain and bone marrow tumours. Their use at the time of surgery improves survival in good performance status patients (Karnovsky  $\geq$  70) by 2.5 months compared to placebo. There is no survival benefit in recurrent high-grade glioma. The main side effects are cerebral infections, CSF leak, cerebral oedema and healing abnormalities, and this is why not everyone uses them (Hart et al, 2011).

**Temozolomide.** Temozolomide is used routinely as adjuvant chemotherapy for high grades. It improves survival and time to progression, without any increase in adverse events. Tumour tissue is analysed for O-6-methylguanine-DNA methyltransferase (MGMT) expression, as this enzyme diminishes the therapeutic efficacy and thus these patients receive little benefit from temozolomide (Theeler, 2011).

**New treatments.** *Bevacizumab* is a humanised monoclonal antibody against vascular endothelial growth factor (VEGF), necessary for tumour angiogenesis. Although there is no level 1 evidence yet, there have been impressive results of progression free survival in some cases in patients with recurrent high grade glioma (Iwamoto & Fine, 2010; Friedman et al, 2009). With the advent of new treatments beginning to improve outcome, this raises questions about reoperation for high grade gliomas. This is a controversial topic, with views across the spectrum. The advantages of reoperation are (i) it has been shown to extend survival compared with medical treatment alone and (ii) it allows for direct local delivery of chemotherapeutic agents. The disadvantages of reoperation are more time spent in hospital, and increased risk of complications, which may outweigh a potential survival benefit. (Brandes et al, 1999; Niyazi et al, 2011). Given that oncologists have more treatments to give

after reoperation, perhaps we should be considering a larger role for surgery and redbulking in recurrent high-grade glioma.



Fig. 5. Neuronavigation Stealth.

**Glioblastoma subtypes.** Gliosarcoma may metastasise extracranially. There are distinct gross macroscopic features described: a firm, well circumscribed lesion; and an infiltrative poorly defined lesion. Treatment and prognosis is similar as for GBM (Han et al, 2010). Giant cell GBM, another rare subtype, is treated in a similar fashion. Data suggests prognosis may be better in this subgroup compared to GBMs as a whole, especially considering long term survival (Kozak & Moody, 2009).

### 3.2 Grade II astrocytomas and oligoastrocytomas

There is no gold standard of treatment and management is controversial ranging from a wait and see policy with serial imaging, to biopsy, to maximal debulking. The role and timing of adjuvant radiotherapy and chemotherapy is also unclear, and is currently being investigated. There are 5 prognostic features which indicate a high risk low grade gliomas: astrocytoma histology, age over 40 years, tumours over 6cm, tumour crossing the midline, and presence of a neurological deficit. Some surgeons advocate resection followed by radiotherapy for these high risk patients (Pignatti et al, 2002; Ruiz & Lesser, 2009).

Awake surgery is well-established for low grade gliomas. The patient undergoes a general anaesthetic for the craniotomy, and is woken when the tumour is exposed. The anaesthetist runs through relevant tests of speech or motor function whilst the gyri adjacent to the tumour are stimulated to map the sensorimotor cortex. It is evident if eloquent brain is involved, as the patient may transiently become dysphasic, develop a motor weakness or experience a sensation down a limb. The surgeon is therefore able to map and avoid resection of this eloquent brain. The patient must be able to understand the procedure and tolerate surgery awake; the patient must be able to cooperate; the tumour should be close to eloquent motor or speech areas which can be tested adequately intraoperatively by stimulation and testing function; the patient must be a suitable candidate for and has consented to adjuvant treatment, as awake surgery in itself would otherwise be ineffective; at least 90% tumour resection is anticipated. There have only been two small prospective randomised controlled studies directly comparing awake versus asleep craniotomy for intrinsic brain lesions. There appears to be no difference in outcome at 3 and 6 months (Ali et al, 2009; Gupta et al, 2007). However the long term results, which are more important, are not known.

Intraoperatively low-grade tumours can look and feel almost like normal brain. A slight discolouration may indicate tumour or brain swelling and it is often difficult to differentiate between the two. Again, surgical experience is required to judge when to stop. Intraoperative MRI is a tool aimed at maximising tumour resection. Although intraoperative MRI has been shown to improve the percentage of tumour resected, its use can be very time-consuming and there is currently no data available to show improved survival benefit (Senft et al, 2010).

The different histological subtypes of grade II gliomas are described in table 1. The variants are not prognostically important, except the gemistocytic subtype (Greek word meaning stuffed cells). These tumours behave more aggressively than their grade suggests and most oncologists will therefore treat these patients with radiotherapy and chemotherapy upfront (Krouwer et al, 1991).

### 3.3 Grade I pilocytic astrocytoma

These often benign lesions comprise of a cyst and solid component. The solid component often enhances, and, is the exception to the rule, in that enhancement does not

mean malignancy. They are found mostly in children and occasionally in young adults, and are located most commonly in the posterior fossa. Pilocytic astrocytoma is not a diffuse tumour. Supratentorial pilocytic astrocytomas tend to be more aggressive. Pilocytic is a Greek word meaning "hairlike," so called due the appearance of the cells under a microscope. An important surgical point to note is that the cyst wall is not part of the tumour. Attempted maximal resection of the solid component is often curative without the need for other treatment. If there is complete removal in infratentorial lesions, there is no need for long term follow up however the presence of worrying features eg supratentorial, or evidence of growth, serial MR are recommended (Fernandez et al, 2003; Krieger et al, 1997).

### **3.4 Rare grade I gliomas: Pleomorphic xanthoastrocytoma, desmoplastic cerebral astrocytoma of infancy and subependymal giant cell astrocytoma (SEGA)**

Pleomorphic xanthoastrocytomas are most often benign tumours that tend to present in patients under the age of 30, with seizures in the majority of cases. Intraoperatively they are often well defined and in close meningeal contact (Van Rooset et al, 1996). Desmoplastic astrocytoma of infancy is a rare subtype that presents as a large hemispheric mass in infants. Radiological features are typically of a large enhancing mass with a peripheral dural based component and a central cystic component. Despite worrisome features, these tumours respond to gross total resection and prognosis is generally favourable (Serra et al, 1996; Uro-Coste et al, 2010). Subependymal giant cell astrocytomas (SEGA), part of the Tuberous Sclerosis complex, are slow growing, benign intraventricular lesions. Historically, surgical resection has been advocated however medical treatment with the mTor inhibitor Everolimus has been shown to reduce tumour size with good seizure control, and may become the hallmark of treatment for these tumours (Krueger et al, 2010; Sharma et al, 2004).

### **3.5 Oligodendroglioma**

These WHO grade II lesions tend to be more benign, and have characteristic appearances of intralésional calcification on CT. Extensive resection followed by a watch and wait policy is an accepted treatment. 1p19q codeletion is a predictor of chemosensitivity and of improved prognosis in these tumours (Thiessen et al, 2003). Anaplastic variants should have adjuvant chemo/radiotherapy (Quon & Abdulkarim, 2008).

### **3.6 Ependymoma**

These tumours are located predominantly in the posterior fossa and commonly present with obstructive hydrocephalus. Treatment is surgical resection followed by radiotherapy (Reni et al, 2007; Stuben et al, 1997). Subependymomas are slow-growing, benign lesions typically found in the ventricular system and may remain asymptomatic throughout life. They are well defined radiologically with little or no enhancement. Given their indolent nature, surgery should err on the side of caution i.e. on leaving tumour behind rather than causing a neurological deficit (Ragel et al, 2006).

## **4. Spinal cord gliomas**

Primary malignant spinal cord gliomas are rare, occurring in 0.12 per 100,000 population, with an increase in ependymomas over the past three decades (Hsu et al, 2011). They usually present with progressive symptoms of numbness and tingling and loss of power.



Pain tends to be a prominent presenting feature, its nature of which is constant and poorly localised waking the patient at night, and it often precedes any neurological symptoms. Back pain that wakes the patient up at night without local tenderness is most often caused by an intrinsic tumour, ependymoma or astrocytoma. The signs are of a progressive myelopathy and may lead to a rapid quadri/paraparesis

The most common tumour type is ependymoma, followed by astrocytoma. There are characteristic MRI radiological appearances, which include an intrinsic expansive cord lesion with variable contrast enhancement, and often cystic components. Surgery is the first line treatment in ependymomas, with en bloc resection and primary dural closure if possible. CUSA is employed for resection, as well as the microscope. Gross total resection is associated with a high complication rate but good outcome and low recurrence rates. Extent of resection depends on how stuck the tumour is. Complete resection is only possible if located at the conus and not stuck, or at filum terminale. If stuck at the conus, tumour should be left behind to avoid disabling complications. Although not radiosensitive or chemosensitive, patients can go on for many years without any deterioration. Overall progression free survival is 89% and 84% at 5 and 10 years respectively (Kucia et al, 2010). Tumours are technically more difficult if higher than conus medullaris, although it still may be possible to remove completely. Intraoperative use of somatosensory evoked potentials and motor evoked potentials can help predict and even prevent post operative neurological deficit, although they may add to length of operation (Kearse et al, 1993; Kelleher et al, 2008). Low-grade astrocytomas are less curable with approximately 50% gross total resection and favourable survival outcome. Little is known about them as they are rare (Benes et al, 2009; Nakamura et al, 2008). High-grade spinal cord tumours (grade III astrocytomas and glioblastoma multiforme) carry a far worse prognosis. Given the rare nature of these tumours, actual outcome is again not known, and no centre has extensive experience. Retrospective studies have shown gross total resection is rarely possible, and most patients die of disease progression. Mean survival is quoted at 6 - 19 months for grade III and IV spinal cord gliomas. Therefore these tumours are probably just as lethal as their brain counterparts (Cohen et al, 1989; McGirt et al, 2008; Raco et al, 2010). Treatment is the same with debulking, radiotherapy and temozolomide, but often an extensive debulking as with brain GBM is not possible, and the maximum amount of targeted radiotherapy is also less than with brain GBM. For these two reasons - less debulking, less radiotherapy - the outcome of spinal cord GBM is probably worse than the outcome of brain GBM. One intriguing possibility that has yet to be explored is to remove the tumour en bloc with a margin of cord above and below. Obviously this would only be possible in thoracic region, and in a patient with no neurological function below the level of tumour. The theoretical advantage would be improved survival benefit. A theoretical disadvantage would be to convert a spastic paraplegia to a flaccid one.

## 5. Paediatric gliomas

Malignant non brain stem gliomas represent 8-10% of paediatric CNS tumours (Hargrave 2009). It is likely the molecular biology of childhood GBM is similar to that of adult GBM, however this is not as well described in the paediatric population. They are usually located supratentorially, but unlike adults, high grade gliomas are significantly less common than low grades (Pollack, 1994). As in adults, these are treated with maximal surgical resection followed by chemo/radiotherapy (Spoto et al, 1989). Diffuse intrinsic brain stem gliomas constitute 15-

20% of all CNS tumours in children, and are their main cause of death (Hargrave et al. 2006). These have characteristic radiological appearances that expand the brainstem with an epicentre situated in the pons. They do not benefit from biopsy and radical surgery is impossible. In exophytic and focal brain stem gliomas, however, surgery is the treatment of choice with radiotherapy reserved for recurrence. The prognosis is better, with 90% alive at 2 years, compared to 25% alive at 2 years in the diffuse group (Mauffrey, 2006).

## 6. Conclusion

In this Chapter we discussed the commonest types of brain tumour, the gliomas. Surgery is an important aspect of the management of these tumours but the extent of surgical involvement remains controversial. Unfortunately little progress has been made in this field over the last 20 years such that the outlook of patients with gliomas has not substantially improved over this period.

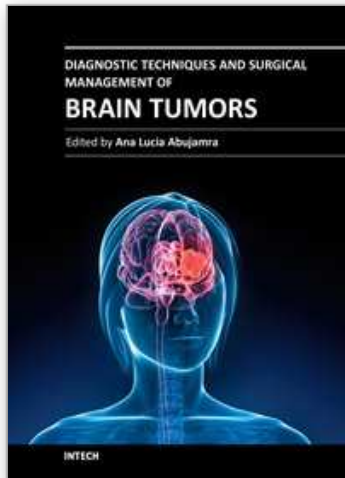
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