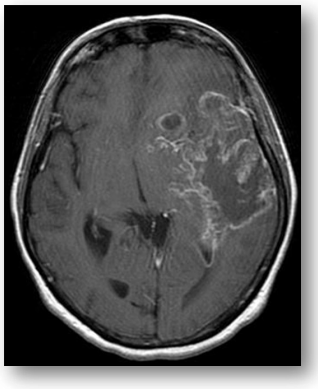
medical student **focus**

Neuro-oncology

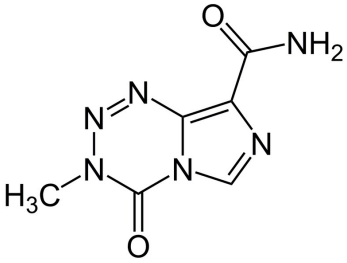
Welcome to the neuro-oncology clinic. In this clinic, we see mainly new patients with a range of brain and spinal tumours to offer nonsurgical treatment (i.e. radiotherapy and chemotherapy). Whilst the treatment modalities offered for different tumours might be similar, the goals of treatment can be very different. It is helpful to see patients with a range of conditions in our clinic if time permits.

High grade gliomas (HGG)

HGG are the commonest form of adult primary brain tumour, and are responsible for a significant part of our workload. The commonest form is the highly aggressive Glioblastoma (See Box 1). These tumours have low potential for metastatic spread, but spread widely through the brain, typically along white matter tracts. They are also relatively resistant to radiotherapy, and for these reasons, the median survival for patients with this disease is in the order of 10-12 months. For the fittest patients we offer combined radical chemo-radiation treatment which improves median survival to 18 months and nearly triples the chances of survival to two years. This treatment is offered to performance status 0-1 patients (See Box 3) with no neurological deficits, and commits them to 6 weeks of radiotherapy treatment with daily Temozolomide chemotherapy (Box 3), followed by 6 months of chemotherapy.



***Box 1** : T1 weighted MRI scan of an aggressive glioblastoma. Note the complex pattern of enhancement*



***Box 2**: Temozolomide. An alkylating agent designed in Cambridge.*

Patients who are less fit, or with neurological deficit, have a poorer prognosis, often in the region of 6 months or less. For these patients we offer a short course of radiotherapy treatment given in 6 visits over 2 weeks, allowing patients to get home with appropriate packages of care. The decision to offer short course or radical radiotherapy can be difficult and emotive, and you may witness the dilemmas faced by patients during their new patient interview. For all patients, it is important to address other issues, such as symptom control, seizures, side-effects of therapy (especially corticosteroids), return to work, and driving status.

Meningioma

At the opposite end of the spectrum are meningioma. These are benign tumours arising from the meningeal lining of the brain, which typically grow and displace adjacent structures. Despite their pathologically benign nature, these tumours can cause severe and life threatening symptoms, depending on their location and the function of the brain tissue being compressed. Meningiomas are usually treated by surgical removal, and in convexity meningiomas on the upper surface of the brain, this is usually the mainstay of treatment. However, meningiomas often occur on the skull base, and become closely apposed to nerves and vascular structures as they exit the skull base. In this situation, the surgeon may not be able to resect the tumour in its entirety without causing significant neurological injury. We know that the extent of resection, graded on the Simpson criteria, is indicative of the risk of disease recurrence (Box 3).

0 - Asymptomatic

1 - Symptomatic but completely ambulatory

2 - Symptomatic, <50% in bed during the day

3 - Symptomatic, >50% in bed, but not bedbound

4 - Bedbound

***Box 3** : World Health Organisation performance status classification*

Grade I : Complete removal including resection of underlying bone and associated dura. *10 year recurrence rate 9%.*

Grade II : Complete removal + coagulation of dural attachment. *10 year recurrence rate 29%*

Grade III : Complete removal w/o resection of dura or coagulation . *10 year recurrence rate 29%*

Grade IV : Subtotal resection. *10 year recurrence rate 40%*

***Box 4**: Simpson Classification for extent of meningioma resection*

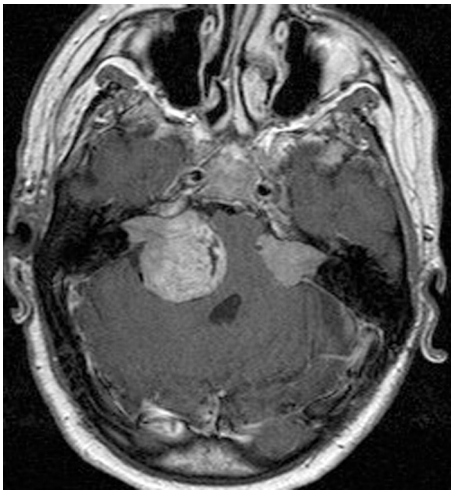
We tend to offer post-operative radiotherapy to atypical and malignant meningiomas, and to low grade meningiomas where the surgeon feels that further surgery would

not be possible if the tumour were to recur. The complex anatomy of the skull base makes radiotherapy treatment planning challenging. If you get a chance to see treatment planning for a skull base meningioma you will gain an understanding for some of the technical aspects of radiation therapy.

Meningiomas are slow growing tumours, and recurrence typically takes place over years. When discussing treatment with patients it is very important to consider the late effects of radiotherapy, specifically the risk of visual impairment for tumours near the optic apparatus, the risk of pituitary insufficiency, and the risk of a radiation induced tumour.

Vestibular Schwannoma

Vestibular Schwannoma (also known as acoustic neuroma) are another form of benign intracranial tumour seen in our clinic, and in the multidisciplinary skull base clinic attended by Dr Jefferies. Remember that these tumours arise from the excess production of Schwann cells which wrap round the 8th cranial nerve. As the tumour grows, it can compress the vestibular and cochlear nerves causing sensorineural hearing loss, tinnitus and balance impairment. As it enlarges further the tumour may protrude from the internal auditory meatus and compress the brain stem and cerebellum, as well as affecting the function of the Facial and trigeminal nerves.



***Box 5**: Gadolinium enhanced MRI scan showing bilateral VS. This appearance is pathognomonic of Neurofibromatosis type II*

Again, although these tumours are histologically benign and slow growing, brain stem compression can be life-threatening. Most sporadic acoustic neuromas occur in the 5th and 6th decade of life. Remember that patients with Neurofibromatosis type II (NF2) can get bilateral acoustic neuromas at a much earlier age as well as multiple meningiomas. For NF patients, there are some specific treatment challenges.

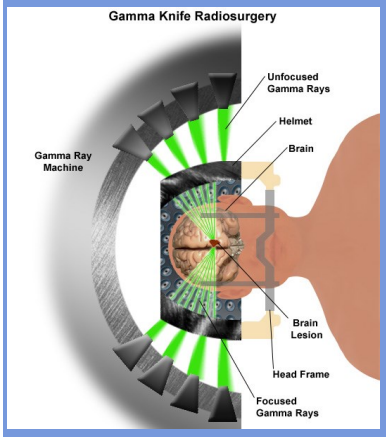
Patients face the decision between surgery and radiotherapy treatment for their tumours. Radiotherapy can take the form of stereotactic radiosurgery, or fractionated stereotactic radiotherapy (see Box 6). Each treatment has pros and cons, but there is no treatment that is clearly superior to the other. For this reason the patients must make their decision based on their own situation. Patients are often very well informed and come with a long list of questions they wish to ask about the radiotherapy treatments available. It is very important to have an understanding of the patient's agenda at the interview, and ensure if possible that their agenda is addressed by the end of the consultation.

VS associated with Some patients with NF2 will develop tumour recurrence after surgery and radiotherapy, with tumour growth rates exceeding 40% every year. For younger patients, surgery for a growing VS may bring the threat of complete deafness. On the basis that VS is a highly vascular tumour, a study was performed in 2010 using anti-angiogenic therapy to control tumour growth.

Box 6 : Radiotherapy Jargon

Fractionated stereotactic radiotherapy (FSRT) : This is high precision radiotherapy given using a linear accelerator where treatment if broken up into a number of daily fractions (usually 30).

Stereotactic Radiosurgery (SRT or SRS) : This is high precision radiotherapy given in a single treatment. The aim is to ablate all tumour cells within the target by giving a very high dose of radiation. This ca be delivered using a conventional linear accelerator, or using one of the two more specialised devices:



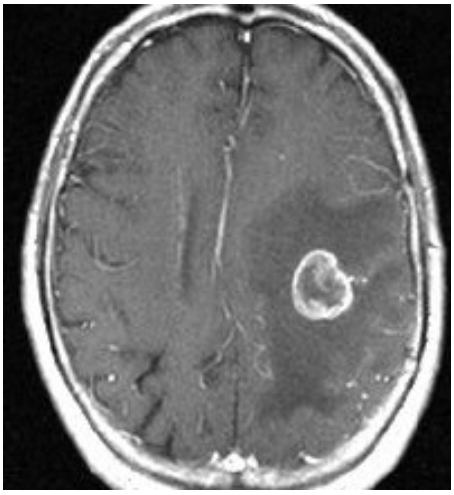
Gamma Knife : A specialised device for delivering SRS in the brain, using multiple tightly focussed radioactive sources to deliver a high radiation dose to the treatment target.

Cyberknife : a device which uses a robotic arm to move a small linear accelerator around the patient,, delivering focussed radiation beams from many different angles. The machine can be linked to organ motion in the thorax, making this technique suitable for radiosurgery in the lung and in the liver.

The results showed impressive rates of tumour stabilisation and hearing preservation in these patients, and we are now able to offer F2 patients treatment with Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF-A). Starving the tumour of blood supply does not get rid of the tumour, but does halt its growth and improve symptoms for patients.

Cerebral Metastases

With the evolution of systemic therapies for a range of cancers, we are increasingly seeing patients who survive for longer periods of time, even with metastatic disease. As a result, patients who develop solitary brain metastases are often referred for consideration of either surgical resection (metastasectomy) or ablative radiosurgery. We typically accept patients with solitary mets less than 30mm in size, having a breast, lung or renal primary and with controlled metastatic disease outside the brain. It is also important that patients can be offered further systemic treatment after radiosurgery. We offer stereotactic radiosurgery to patients using the Tomotherapy system, as it allows us to image the patient before, during, and after treatment to ensure that the area of intense radiation dose is correctly positioned within the brain.

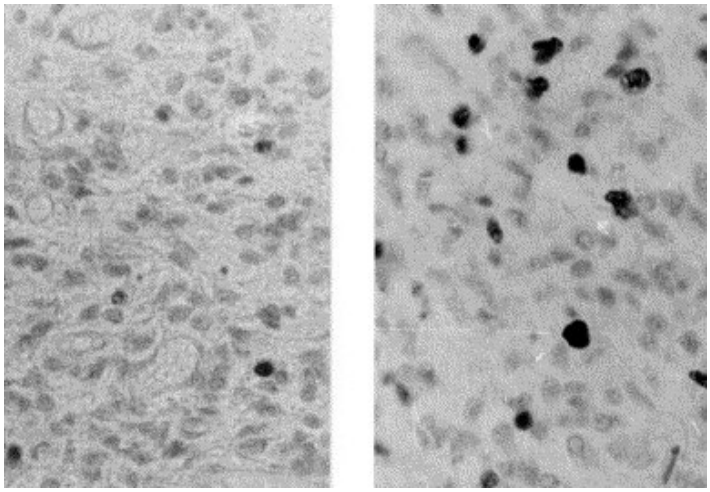


***Box 7**: Gadolinium enhanced MRI scan showing a solitary metastasis in a patient with breast cancer. The tumour is quite deep seated and in eloquent cortex, making surgical excision less attractive.*

What is so important about MIB?

Finally, you may notice in discussion about a whole range of tumour that the oncologists are discussing the MIB count of the tumour. What does it mean and why is it so important?

MIB is short for MIB-1, an antibody directly against the nuclear protein Ki-67. Ki-67 you may recall is associated with cellular proliferation, because it is present during G1, S and G2 phases of the cell cycle, but is absent during G0. The pathologist will use Ki-67 to quantify what proportion (or percentage) of the tumour cells are actually undergoing proliferation. Mib-1 works across a whole range of tumours. Benign meningioma may exhibit a Mib index of 1%, whereas Burkitt's Lymphoma, one of the most rapidly proliferating solid tumours, is usually associated with Mib indices of 80% or higher.



***Box 8**: Mib-1 staining of two high grade gliomas of two anaplastic astrocytomas. The one of the left has a small number of cells exhibiting Mib-1 staining, consistent with a grade 3 tumour. The one on the right has a higher proliferative rate, in keeping with a glioblastoma.*

We use Mib as an adjunct to the WHO grading of tumours. Strictly, WHO grading of tumours is based on histological and cytological features that can be seen using standard H&E staining. However we know that Mib labelling index is an independent prognostic factor in most tumours we encounter. For example, a Grade 3 anaplastic astrocytoma (AA) will typically have a Mib index in the range of 5-10%. If we see a tumour which has histological features of a grade 3 AA which has a Mib index of 38%, we would be worried that this tumour would behave like a Glioblastoma, and treat it accordingly (See Box 8).

Conclusion

I hope this document will set the scene for the patients we typically see if our clinic. Please do not hesitate to ask us if you do have any questions about anything that you see or hear about in our clinic.

Raj Jena. March 2013