Glioblastoma multiforme:

Glioblastoma multiforme (GBM WHO grade IV) is the most commonly occurring and most malignant brain tumour, characterised by extensive infiltration of the brain. Although there is no clear explanation as to what causes a GBM, certain genetic predispositions do appear to play a role, and prior exposure of the brain to ionising radiation has been associated with significantly higher rates of occurrence of gliomas.

The prognosis of GBM is unfortunately uniformly poor, and treatment is therefore centred primarily on maintenance of quality of life. First diagnosis is not unusually made when the tumour has already reached significant proportions, as it is often the case that patients become symptomatic only then. Without treatment, survival is typically up to three months from the time of diagnosis. With optimal multi-modal treatment the median survival time for the vast majority is about one year. Younger age, gross debulking and better general condition appear to be favourable factors for a longer survival time.

A GBM may be primary, when it is arising directly as a Grade IV glioma, or secondary, arising from a Grade II or III glioma. Primary GBM develops more commonly in older patients, while secondary GBM develops more commonly in younger patients. Although the majority of GBM cases are registered from the fourth decade of life onwards, brainstem GBM is a paediatric malignancy, occurring most often in the very young. The time taken for progression from a lower grade glioma to a GBM is variable, ranging from several months to more than a decade, with a mean interval of about 5 years.

The current treatment strategy consists of maximum possible reduction of tumour bulk without causing fresh neurological deficit, followed by combined radio-chemotherapy with TMZ over a six weeks period followed by six months of adjuvant chemotherapy with TMZ on a four weekly cycle. Surgical removal of the tumour is never "complete" per se, as even "gross total resection" implies removal of only what can be identified in neuroradiological films and under the microscope, while real tumour borders typically extend beyond visibility — besides, the extent of tumour removal depends on the location and the presence and topographical relevance of "eloquent" areas.

Adjuvant treatment is aimed to start in a time frame around 4 weeks after surgery, assuming the underlying clinical condition allows the

start of the combined modality treatment with radiotherapy and chemotherapy. Given that any remaining tumour after an operation can still grow after the commencement of radiotherapy/chemotherapy, it is not uncommon to see in some patients an increase in the residual tumour size at the 1st post-radiotherapy baseline scan (pseudo-progression). It is very difficult even with all available current imaging modalities to separate this from true progression and hence the decision about further management will have to be made on an individual basis, based on the patients' signs and symptoms, radiological appearances and the local clinician's assessment.

Careful surveillance with serial MRI or CT scans is a crucial part of medical care, because tumour regrowth requires alteration of current treatment or, for patients in the observation phase, restarting treatment.

A regime for combined radio-chemotherapy following surgery is as follows:

Radiation:

- Tumour site along with a security margin: 30 sessions at the rate of 2Gy per fraction for 5 days/week (60Gy in total).

Chemotherapy:

- Temozolomide: Concurrent period with radiotherapy: from Day 1-42 at the rate 75mg/m2 by mouth on an empty stomach (1 hour before or 3 hours after a meal) once a day for 6 weeks.
- Temozolomide: four weeks break (Day 70)
- Temozolomide: Maintenance period from day 71 (Cycle1): only 5 days per month, every 28 days for 6 months (Cycle 6), at the rate of 150mg/m2 for the first cycle, increased to 200mg/m2 with the second cycle and onward.
- Considering treatment with Temozolomide causes suppression of the bone marrow, a blood count ought to be performed weekly during the period of combined radio-chemotherapy, and then at day 1 of each cycle thereafter.

Recurrences may either be local at the site of first occurrence, or in other areas of the brain. The treatment of recurrences needs to be tailored to the individual case, keeping the patient's general condition in perspective, because of the possible risk of iatrogenic

neurotoxicity. Besides best supportive care if the performance status (PS) is poor, repeated surgery in the case of local GBM or for symptomatic large lesions can be an option as well as systemic chemotherapy with Bevacizumab (this drug has been approved by the FDA in USA but is not registered in UK) +/- chemotherapy (CPT-11,BCNU, TMZ); PCV, TMZ, Nitrosourea, platinum based regimens and Cyclophosphamide. It is also possible to consider re-irradiation in selected cases with:

- Stereotactic brachytherapy: that involves stereotactic placement of radioactive isotopes directly within the brain tumor, thereby minimizing possible harm to normal brain tissue or
- Stereotactic radiosurgery: that may be used to treat small, well-defined lesions using stereotactically guided delivery of a single high-dose of radiation.