Update on the management of CNS tumours

Oncology Update
Sobell Study Day 16/11/18
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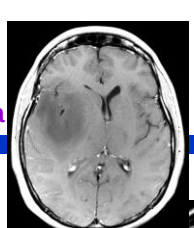
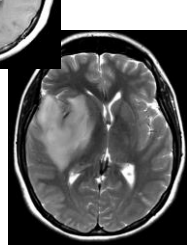
Brain tumours (primary) and brain metastases in adults

- **NICE guideline [NG99] Published date: July 2018**
- https://www.nice.org.uk/guidance/ng99/chapter/rationale-and-impact

Radiology Low Grade Glioma





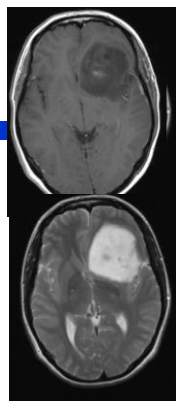
- MRI features
  - Grade 1 pilocytic astrocytoma: ALL enhance
  - **Grade 2 astrocytoma:** Increase T2 is all tumour, often widespread. Don't enhance. Often v large with mass effect and minimal symptoms

Glial Tumours

- Diffuse Grade 2 astro or oligo
  - Astrocytoma
    - IDH Mutated
    - IDH wildtype
    - NOS
  - Oligodendroglioma
    - IDH Mutated, **1p19q codeleted**
    - NOS

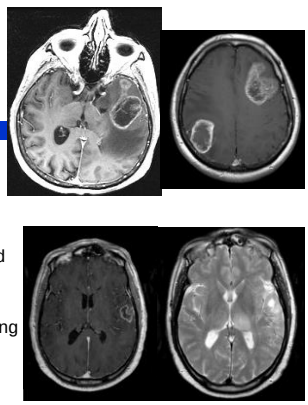
- Others astrocytic
  - PA
  - PMA
  - SEGA
  - PXA
  - APXA
- Other glioma
  - Chordoid
  - Angiocentric
  - astroblastoma

Radiology
Grade 3 Gliomas



- MRI features
  - Grade 3 astrocytoma: 80% enhance, T2 abnormality is all tumour.
  - Note may have G2 progress to G3
  - Oligodendroglioma: Usually calcified, enhancement does always NOT mean anaplastic
- rCVB increase
  - Early Indication of high grade transformation even if noenhancement

Radiology
Grade 4 tumours



- MRI features
  - all enhance
  - Usually significant surrounding oedema
  - Cells up to 2cm beyond enhancing edge
  - May be multifocal
  - May have non enhancing areas

Glial Tumours

- Grade 4.
  - Glioblastoma
    - IDH Mutated
    - IDH wildtype
    - NOS
  - Diffuse midline glioma H3K27M mutated
- Grade 3
  - Anaplastic Astrocytoma
    - IDH Mutated
    - IDH wildtype
    - NOS
  - Anaplastic Oligodendroglioma
    - IDH Mutated**, 1p19q codeleted**
    - NOS

Histologic Genetic features

- IDH1 or IDH 2 mutation.
- disrupts control of histone methylation
- Better prognosis
  - Grade 2 astro +oligo – 80%
  - Grade 3 astro + oligo – 80%
  - Grade 4 GBM
    - Primary – IDH 1 not seen
    - Secondary – common
    - >60 years – not seen

- Methylation of MGMT
- Disrupts methylation
- Better prognosis
  - Grade 2 astro – 80%
  - Grade 2 oligo - most
  - Grade 3 astro – 50%
  - Grade 3 oligo – 70%
  - Grade 4 GBM - 50%

Implications of genetic changes

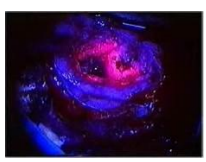
- 1DH1 and IDH2 mutation
  - Better prognosis if present – no therapeutic implication
- Meth MGMT
  - Better prognosis if present
  - Indicates higher response to temozolomide (esp GBM > 70)
- 1p19q co-deletion (ONLY Oligodendroglioma)
  - Better prognosis if present
  - predicts higher response to PCV chemo

Medical management

- **Dexamethasone + PPI**
  - post op reduction to nil - (nb not if biopsy only)
  - Try NOT to increase to 16mg with every admission!
- **Antiepileptic**
  - No prophylactic anticonvulsant (no evidence of benefit)
  - If seizures: keppra first line and lamotrigine usually second line
- **VTE –** 20% of HGG **-** use LMWH
- **Antidepressants –** often needed

Surgical management – new techniques

- Stealth guided stereotactic procedures
- Functional imaging before surgery
- 5ALA to highlight tumour - emits blue light

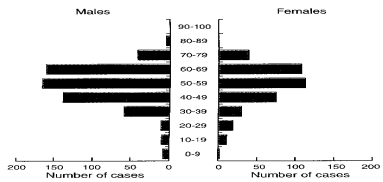


Surgical management – new techniques

- Awake craniotomy with electrocortical stimulation
- Mini-craniotomy and endoscopic debulking
- Aggressive supra-total resection for LGG (T2 tumour + margin) - reduced anaplastic transformation

High Grade Glioma
Incidence and Age Distribution

- Most common type of brain tumour
- Incidence 5 per 10^5 in UK



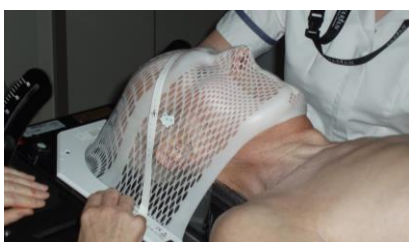
How do we know who will do better?

- Histological grade (grade 3 better than 4)
- Age (less than 45 > less than 65 > over 65)
- Pre-op performance status 0-1 >2>3-4
- Length of history of fits (none = worse prognosis)
- Low grade transformation to high grade
- Extent of resection - >90% resection vs biopsy only

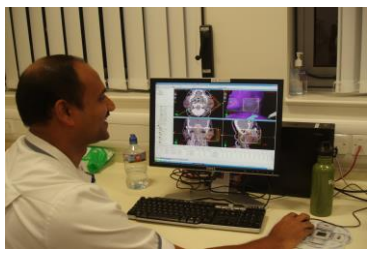
RT treatment for patients with brain tumours

- Treatment
  - 6 – 33 fractions
  - Daily (Mon to Fri)

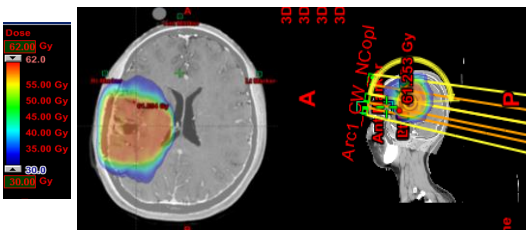
Positioning the patient – conventional mask.



Planning radiotherapy

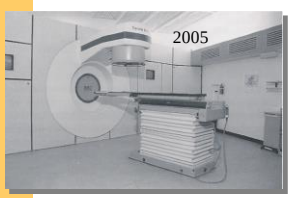


Treatment planning RA IMRT



Radiotherapy Treatment

Linear Accelerators



Treatment delivery

- Radiographers check the patient position (On Board Cone Beam CT or ExacTrac imaging) – 5 – 10 minutes
- Deliver the treatment – 2-5 minutes
  - Conformal Fixed beams from 2-4 angles
  - Intensity Modulated Radiotherapy gives better shaping around the tumour – takes a long time 7-9 beams
  - We use Rapid Arc – 1-3 arcs round the patient – very quick

Radiotherapy – GBM: Indications

- Historic data following biopsy or “resection” (1978)
  - BTCG (Walker J Neurosurg 1978) Med Surv 1 yr Surv
    - Surgery + steroids **14 weeks** 3%
    - Surgery + 50-60Gy WBRT **35 weeks**
- Current standard: age 18 – 70 years PS=0-1:
  - **Radical treatment RT + Temozolomide after resection or biopsy only**
  - 60 Gy in 30 # over 6 weeks, then 6 -12 cycles adjuvant temozolomide

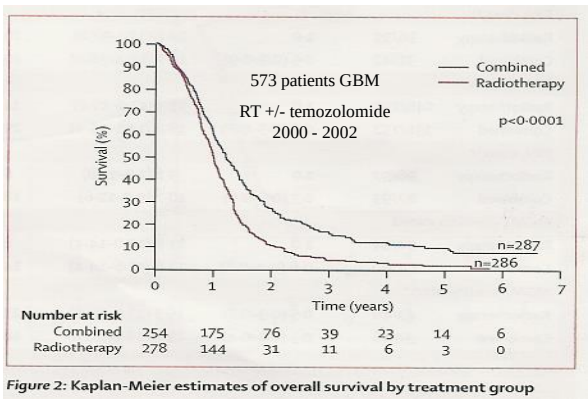


Figure 2: Kaplan-Meier estimates of overall survival by treatment group

Temozolomide

- Cytotoxicity of temozolomide is mediated mainly through methylation of the O6 position of guanine
- This DNA damage is rapidly repaired by MGMT
- Methylation of the MGMT gene increases sensitivity to Temozolomide (50% of GBM have meth MGMT)

Temozolamide – Side Effects

- Nausea and vomiting
- Constipation (ondansetron)
- Myelosuppression (week 3 – 4)
- Sore mouth
- Fertility impairment
- Rare – rash or Stevens Johnson syndrome
- Generally very well tolerated

Side effects of RT - Early

- Acute
  - skin red, sore, blistering
  - Hair loss
  - Headache
  - nausea
  - fatigue
- Early delayed – transient demyelination due to temporary deletion of oligodendroglia
  - "3 months after RT worse than during"
  - somnolence syndrome

Toxicity of RT - Late

- Occurs 2 to 10 years post RT
- Cerebral changes due to oligodendroglial loss and endothelial damage, cause demyelination & necrosis
  - poor short term memory and concentration
  - Psychomotor speed reduced
  - Dementia, spasticity , seizures - very rare (WBRT,dose)
  - 5% risk of necrosis if >72Gy in <2.5Gy #
  - 50% risk of cognitive decline at 12 years for LGG
  - T2 hyper-intensity on MRI within RT fields.

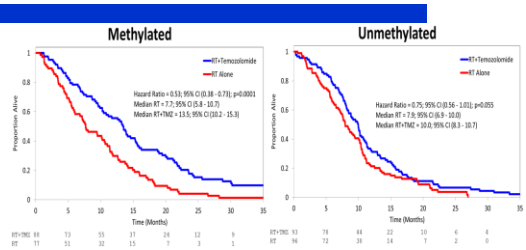
Toxicity of RT - Late

- Impaired short term memory
- Large volume old fashioned RT – reduced mobility and cognitive function (like dementia)
- Permanent hair loss much less with RapidArc
- Pituitary function. (>2 years) – check annually if pituitary in RT volume. Esp if >40Gy
- CVA – 4 x increased relative risk after pituitary RT
- Second malignancy

GBM in >70 year olds

- Hypofractionated RT for over 65 years old
  - **EORTC trial 26981 (Perry) 2016**
    - 40/15 + temozolomide – meth MGMT positive **MS – 13 months**
    - 40/15 alone – meth MGMT negative **MS – 8 months**
- Paradigm study open in Oxford:
  - meth MGMT negative: 40/15+PARP inhibitor /placebo
- Pragmatic about need for biopsy for this group. If not for chemo we don't pursue biopsy and give 34Gy/10 or nothing. PS3-4 - no treatment prognosis 2-3 /12

Overall survival EORTC 26981. >65 RT+/- temozolomide

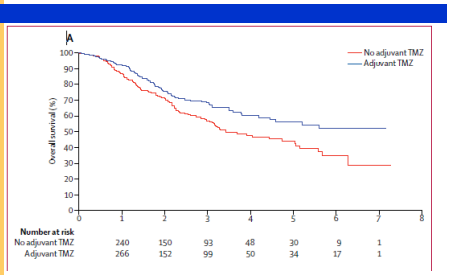


Grade 3 Astrocytoma - management

- CATNON/ BR14 trial – Lancet Oncol 2017
  - Grade 3 tumours with no 1p19Q **(ie Anaplasrtic Astro)**
  - RT + /-temozolomide during RT +/- 12 months temozolomide
- Adjuvant 12 months temozolomide

	% 5 year OS	Median PFS
No (n = 372)	44.1%	19.0 mo
Yes (n = 373)	55.9%	42.8 mo

Overall Survival curve for Adjuvant Temozolomide for Grade 3 astrocytoma



Anaplastic Oligodendroglioma

- RT 59.4 Gy / 33 x 1.8 Gy fractions
- The PCV chemo x 6 cycles from 2 trials
  - EORTC 26951 and RTOG 9402 trials
- survival benefit
  - **MS >12 or 14 years for RT + PCV**
  - **vs**
  - **7-9 yrs with RT alone**

Relapse / Progression

- Consider re-operation
  - if good PS (>70%)
  - mass effect or cyst for aspiration
  - median survival 14 -36 weeks from re-operation
- Consider chemotherapy
- Otherwise
  - Ensure that patient is on lowest possible dose of steroids
  - Assess/ arrange palliative care involvement with GP / hospice

Chemotherapy in Relapsed HGG

- Our policy:
- Re-expose to temozolomide if initial response and >3 months treatment free (gives a 30% 6 months PFS)
- Lomustine chemotherapy if <3 months or not good response – EORTC 26101:BELOB trial 2016 lomustine +/- avastin
- MS = 8-9 months no sig difference.
- Response – about 20%

PCV– Side Effects

- Nausea and vomiting day 1-2 – (significant)
- Rash + photosensitivity (procarbazine)
- Procarbazine interactions (weak MAOI and antabuse)
- Myelosuppresion (week 4-6) – can be profound
- Peripheral neuropathy (vincristine)
- No hair loss
- Infertility

New approaches: Targeting the Vasculature— Anti-angiogenesis in Treatment of GBM

- Neovascularization is a hallmark of GBM
- VEGF mRNA is up to 50 fold overexpressed in GBM
  - VEGF inhibitors (Bevacizumab and Cediranib),
  - Integrin inhibitors which inhibit angiogenesis (Cilengitide)
  -
- However, to date these have not impacted with a survival benefit for these patients in the adjuvant or recurrent setting. (Gilbert 2013, Wick 2013).
- Bevacizumab +/- Irinotecan for relapse post temodal MS 8 months both arms (BRAIN study) – licensed, but not compared with Lomustine

NEW approaches: Immunotherapy…

- DC Vax- autologous tumor lysate-pulsed dendritic cell vaccine
  - Phase 3 trial with 90% of patients receiving DCVax due to crossover on progression…..MS 23 months from surgery trial outcomes not yet announced. (NB exclusion if progression after surgery +RT)..
- Ipilimumab – CTLA4 inhibitor – promotes T cell
  - Phase 3 trial IpiGlio – about to start in Oxford. Adjuvant Ipi

Low grade glioma – benefits of RT

- 50% of patients - tumour shrinkage > 50%
- Some patients – improved epilepsy control
- CTV = region of T2 intensity + 1cm.
- 60% 5 year survival if RT given initially or on disease progression
- 14 month improvement in progression free survival

LGG 5 prognostic factors

- age > 40,
- astrocytoma subtype,
- tumours > 6cm,
- those crossing midline, and
- presence of neurologic deficit before surgery are poor prognostic features.

- High risk (>=3) MS 3 years
- Low risk (0-2) MS >7 years

Outcome High risk LGG RT +/- PCV

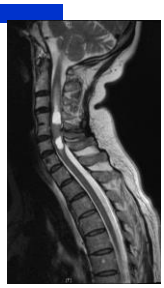
	Overall survival		
	Median	% 5 year	%10yr
RT (n = 126)	7.8 years	63.1%	40.1%
RT+PCV (n = 125)	**13.3years**	**72.3%**	**60.1%**

Bruckner RTOG NEJM 2016.

Low Grade glioma (astrocytoma or oligodendroglioma) at high risk of recurrence should have RT + PCV chemo following surgery…….

Ependymoma

- Low grade
  - Local RT (50 – 55 Gy) if unresectable or partially resected.
  - Myxopapillary ependymoma – v good prognosis. (no RT)
- Anaplastic grade 3
  - Stage spine (MRI + CSF)
  - If CSF/MRI + - Craniospinal RT
  - MRI or CSF neg Local RT only (54 – 59.4Gy)



Radiotherapy for Benign Tumours

- Consider if
  - incomplete excision
  - Unresectable
  - Symptomatic (eg acromegaly not controlled with med)
- Pituitary adenoma
- Meningioma: G1, G2 recurrent or critical site. G3 all RT
- Craniopharyngioma usually cyst drain + RT
- Vestibular Schwannoma (SRS)
- Cordoma/chondrosarcoma – Proton

Stereotactic RT

- RT technique
  - Precision immobilisation and RT delivery
- Fractionation
  - Single radiation treatment (radiosurgery - RS)
  - 2 – 5 fractions (stereotactic RT - SRT)
  - >5 fractions fSRT (eg skull base meningioma)

Aims

- Achieve uniform dose homogeneity within planning target volume
- Minimise dose to surrounding normal tissue.
  - Rapid dose all off at the field edge - typical distance from 90% to 50% is a 1-3 mm
  - Low dose exposure ? related to RT induced malignancy so should be reduced in CNS and trunk

SRS

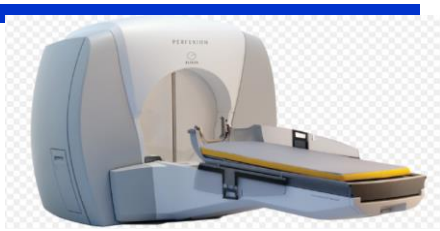
- Linac-based
- Gamma Knife
- Cyber Knife

- All ways of delivering very high doses of radiation to very small tumours in the brain in a single treatment.
- Many studies comparing techniques/equipment. No clear advantage to any particular one. NHSE has commissioned all three within the UK.

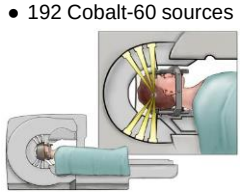
Indications for SRS/RT

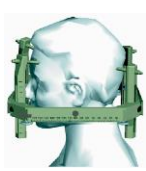
- SRS (single fraction)
  - brain metastases (<20cm3 total volume).
    - Prognosis>6 months, controlled extracranial disease.
    - If close to brain stem can give 5 fraction SRT
  - Vestibular Schwannoma
  - Pituitary adenoma recurrence – if >3mm from chiasm
  - Artereovenous malformations
  - Trigeminal neuralgia
- SRT (conventional fractionated treatment)
  - Meningioma – if near critical structures: esp skull base
  - Pituitary adenoma / craniopharyngioma
  - Chordoma / chondrosarcoma if proton therapy not an option

Gamma Knife



- 192 Cobalt-60 sources



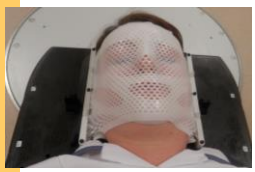


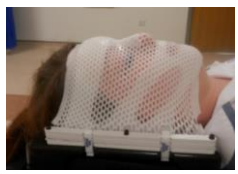
Linac-based

- Linear Accelerator
- ExacTrac imaging
- RapidArc or Dynamic conformal arcs (DCA)

Linac-based

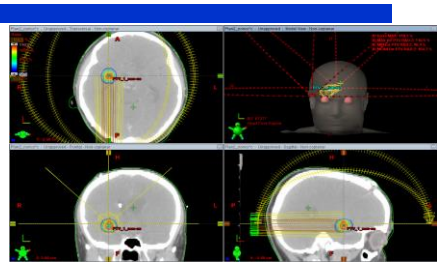
- Mask (frameless radiosurgery)



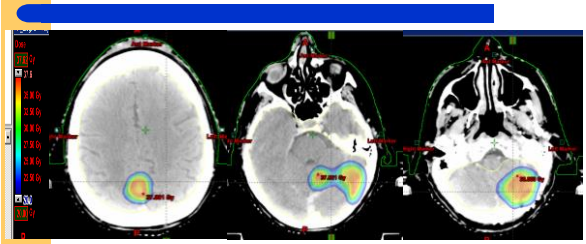


Mask for Linac based Stereotactic Radiosurgery

Treatment planning SRS single fraction



Treatment planning SRT multiple mets treated with 6 Rapid Arcs



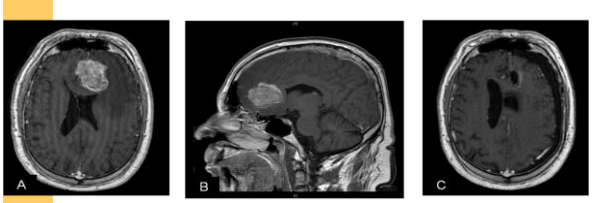
Management of patients with brain metastases

- 40% of cancer patients develop brain metastases
- Steroids alone- Median survival is 2–3 months
- Whole brain radiotherapy (WBRT) median survival is about 3–6 months
  - NB: QUARTZ trial showed no survival benefit to WBRT for lung cancer patients with multiple mets……
- But if patients are good PS, controlled systemic disease consider:
  - Surgery: ms 9-12 months
  - Or SRS: median survival 10-18 months

Which patients are offered surgery?

- Larger brain metastases (>20cm3)
- 1-2 lesions – usually same side of brain
- Clinically relevant mass effect
- Large Posterior fossa mets with risk of hydrocephalus
- In order to obtain histology
- Option; operate on larger lesion, give SRS to smaller ones.
- Key issue: must have controlled systemic disease or a plan to go on to further systemic therapy.

Surgery
Metastatic Melanoma- Endoscope assisted resection



How effective is SRS alone?

- Reported local control rates for patients with small volume brain mets (<20cm3)
  - 90–94% for breast cancer metastases
  - 81–98% for lung cancer
  - 73–90% for melanoma
  - 83–96% for renal cell cancer
  - Overall – approx. **70% local disease control.**
- Progression free survival 4-5 months

Survival

RTOG Recursive Partitioning Analysis (RPA) for brain metastases		Median Survival WBRT	Median Survival SRS
Class I	KPS >=70, <65 years, controlled primary, no extra-cranial metastases.	7.1 months.	18 months
Class II	Neither I nor III	4.2 months	10 months
Class III	KPS <70.	2.3 months	n/a

SRS tolerability

Side effect	Comments
Nausea	Ondansetron 8mg bd x 2 days
Fatigue	Seems quite minor
Hair loss	Patchy if met near scalp
Seizures	1 week after treatment….
Headache	Dex 6mg bd x 2 days (then tail down over 4 days
Radio-necrosis	If Brain – GTV V12Gy is 10cm3. =10% risk (NB if multiple mets max V12Gy < 30cm3

WBRT after SRS or Surgery?

- EORTC trial (Kocher et al JCO 2011)
  - +/- WBRT post surgery (160 pts) or radiosurgery (199 pts)
  - 1 to 3 mets
- Results WBRT vs observation
  - No survival benefit (median survival - 10.9 mo)
  - Delays neurological progression by 1.2 months.
  - Reduces intracranial relapses and neurologic deaths (44% vs 28%)
  - Fails to improve the duration of functional independence

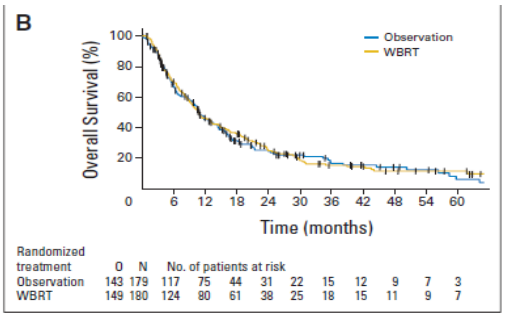
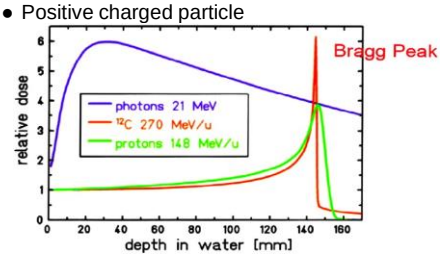


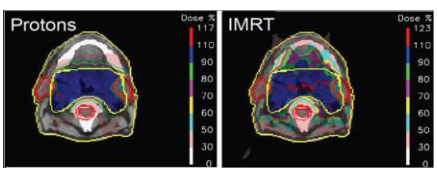
Fig 3. (A) Survival with WHO performance score ≤ 2 and (B) overall survival after observation or adjuvant whole-brain radiotherapy (WBRT). O, number of events; N, number of patients.

Proton therapy

- Positive charged particle



Why protons?



Support for Patients and Relatives

- **CNS CNS, OT , Physio**
- **Histology clinic – rapid oncology appt**
- **Written information sources**
  - Nurse specialist packs given to patients
    - Steroid booklet, epilepsy booklets
    - Brain RT info sheet, chemo MacMillan info sheets
  - patient organisations
    - Brain Tumour Foundation
    - British Brain and Spine Foundation
    - MacMillan
- **Driving**
  - At least 2 years off driving – high grade (3+4) brain mets
  - 1 year off for grade 1,2