CNS TUMOURS:
FROM PRESENTATION TO TREATMENT

The Patient Journey

Allan James
Consultant Clinical Oncologist
Beatson West of Scotland Cancer Centre

The Patient Journey

Conflicting priorities:

- Speed – get onto treatment asap when presenting with a brain tumour
- Optimal management – establishing symptom control, full work-up, accuracy of diagnosis, best surgery, full pathology, referral to appropriate specialist for ongoing therapy, delivery of high quality state-of-the-art treatment

- NB - “Getting your head round it”

The Patient Journey

Background

- Epidemiology

1. Commonest tumour in the brain in adults – metastatic spread: Lung (SCLC > NSCLC), breast (especially *her-2* positive)
2. Across the board, *rare* – 1.5% cancers are ***primary*** brain tumours
3. Incidence of all primary brain tumours – 14/100,000 per year - malignant primary brain tumours, most common intrinsic tumour – glioma – 6-8/100,000
4. Incidence of gliomas =
    - 150-250 in W Scotland each year (catchment - ~2.8m) (all grades)

5. Although the overall incidence varies a little with race and geography, relative incidence of each type of primary brain tumour seems to be uniform worldwide
6. Increasing incidence with age
7. No real known aetiological factors (except ionising radiation)

Figure One: Numbers of new cases and age-specific incidence rates for brain and CNS tumours, by sex, UK, 2003

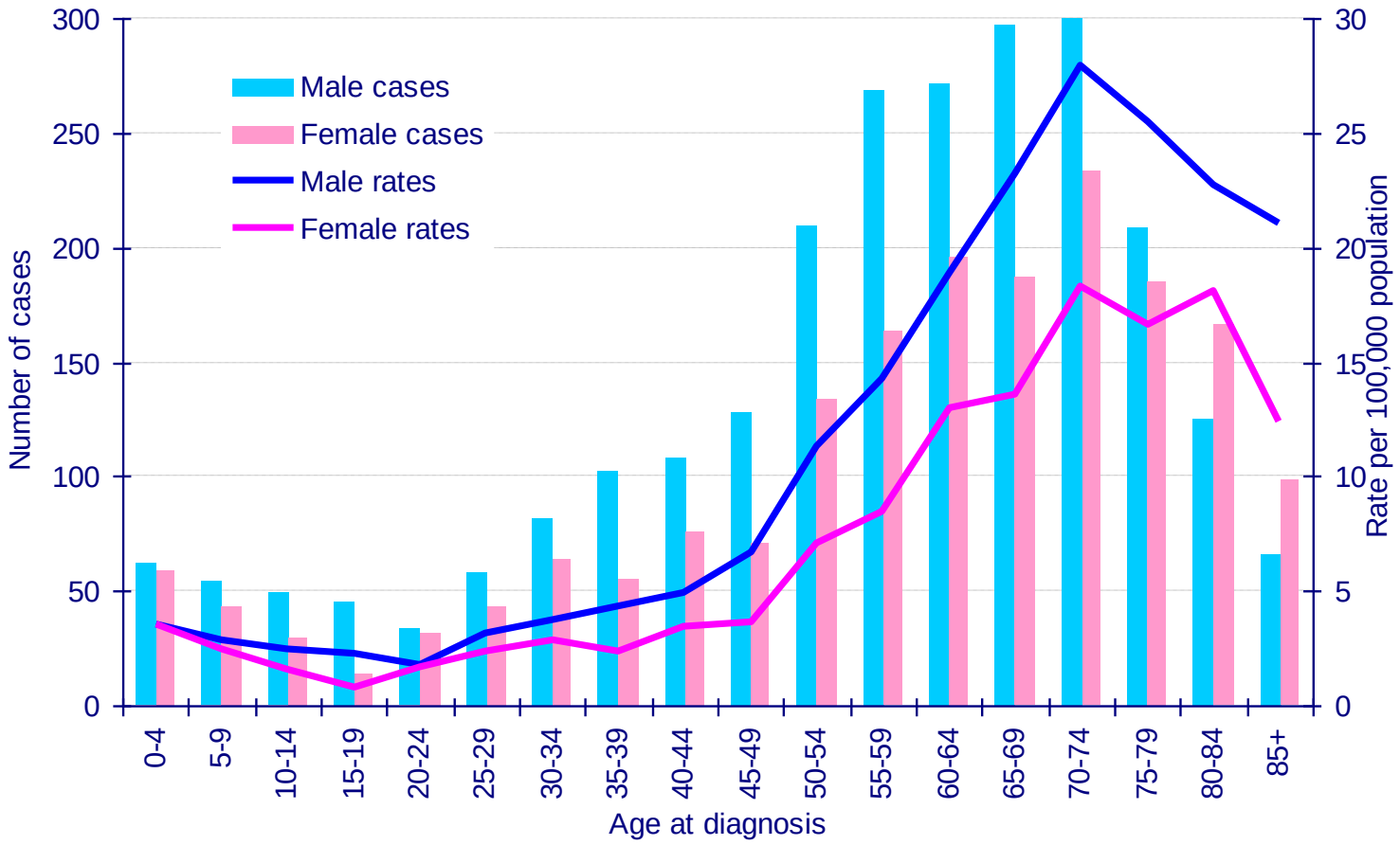
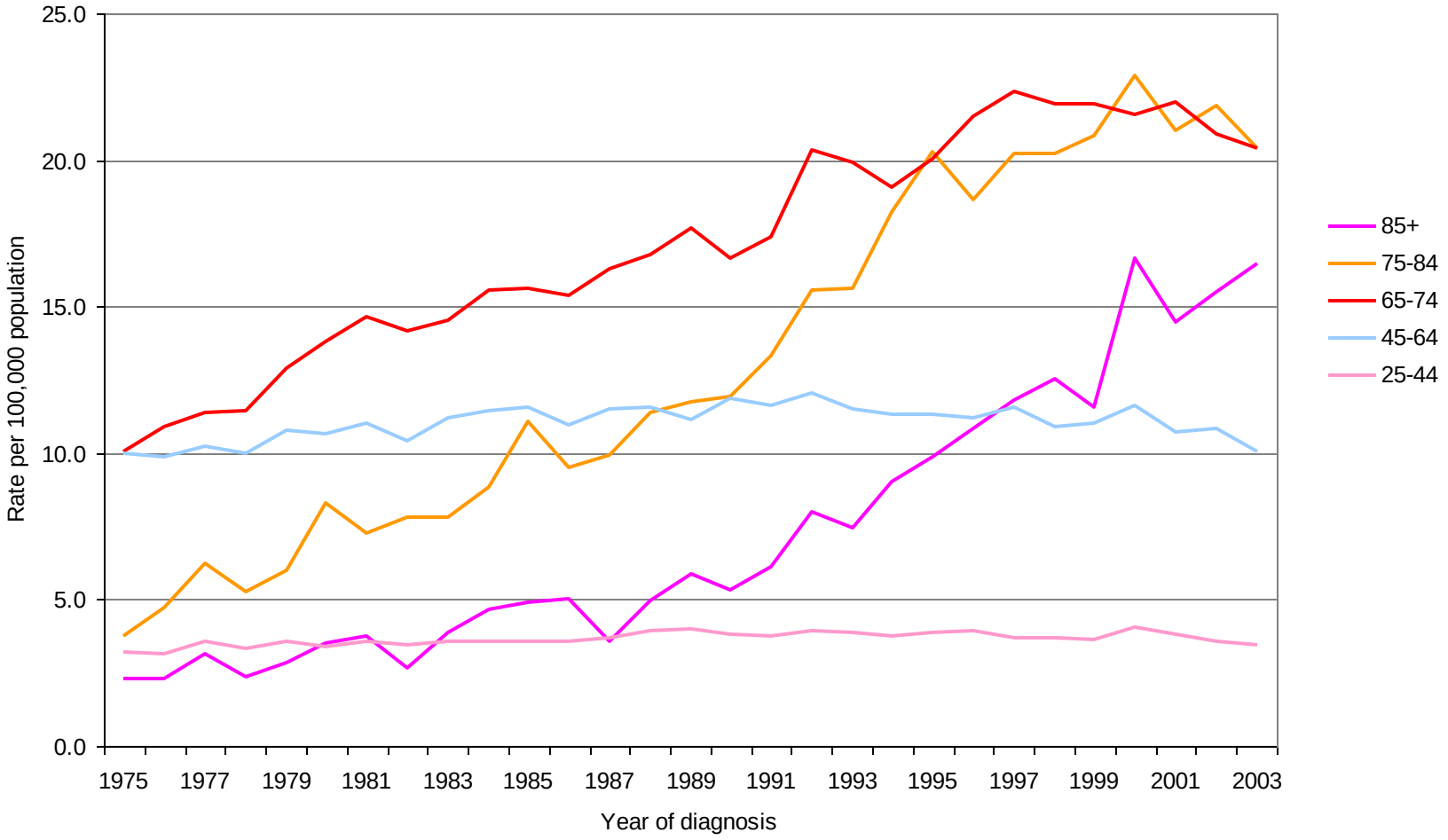


Figure Seven: Age specific incidence rates, brain CNS cancer, persons - GB, 1975-2003



The Patient Journey

Prognostic factors

- ***Age***
- Performance status
- Pathology – grading, type, genetics/molecular information
- Extent of surgery (?)

The Patient Journey

RPA Class	RTOG (original)	EORTC (adapted)
III		
Age, years	< 50	< 50
Tumor type	Anaplastic astrocytomas	Glioblastoma multiforme
Mental status	Abnormal	
PS		WHO PS 0
or		
Age, years	< 50	
Tumor type	Glioblastoma multiforme	
PS	KPS 90-100	
IV		
Age, years	< 50	< 50
Tumor type	Glioblastoma multiforme	Glioblastoma multiforme
PS	KPS < 90	WHO PS 1-2
or		
Age, years	≥50	≥50
Tumor type	Anaplastic astrocytomas	Glioblastoma multiforme
PS	KPS 70-100	
Treatment status	≤3 from time of first symptom to start of treatment	Complete/partial surgery
Mental status		MMSE ≥27
or		
Age, years	≥50	
Tumor type	Glioblastoma multiforme	
Mental status	Good neurologic function	
Treatment status	Surgical resection	
V		
Age, years	≥50	≥50
Tumor type	Glioblastoma multiforme	Glioblastoma multiforme
PS	KPS 70-100	
Mental status	Neurologic function that inhibits the ability to work	MMSE < 27
Treatment status	Surgical resection or biopsy only followed by at least 54.4 Gy radiotherapy	Biopsy only
Or		
Age, years	≥50	
Tumor type	Glioblastoma multiforme	
PS	KPS < 70	
Mental status	Normal	

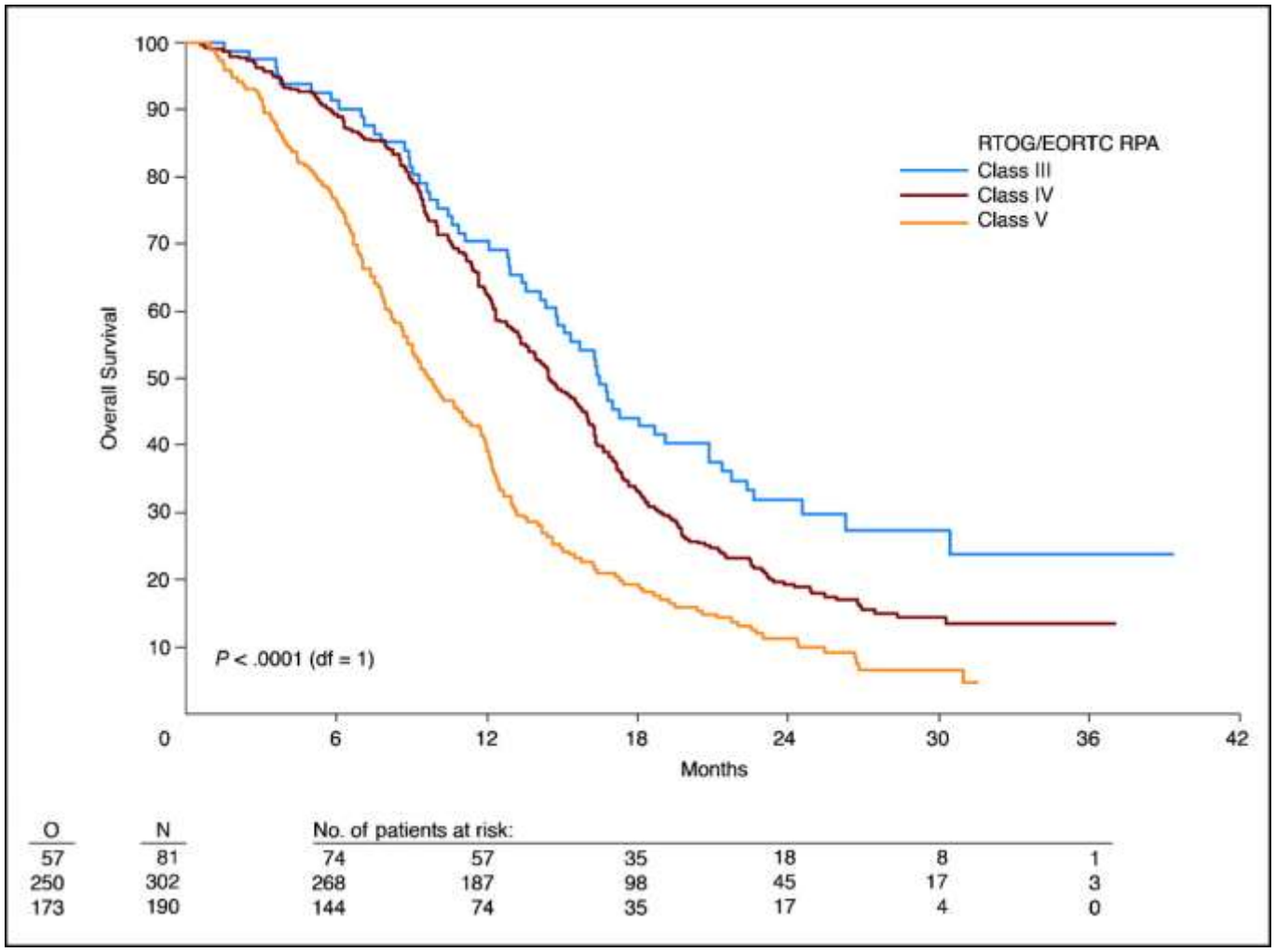
RPA III

RPA IV

RPA V

Prognostic classification of Stupp trial of chemo-XRT in GBM

The Patient Journey



The Patient Journey

- Using clinical information can begin to determine different prognostic groups
- Can be important in determining treatment suitability
- Not very “biological”
- Bio-markers – prognostic and predictive

The Patient Journey

- Therapies
- XRT
- Chemo
- Biological / targetted therapies – disappointing thus far
- Gene therapy
- Immunotherapy – vaccines

- But also –
- Symptomatic – ICP (steroids – must do better), anticonvulsants
- Supportive – OT/PT/Rehab/SW/Palliative care etc etc

The Patient Journey

- Some general issues:
- Single lesions vs multiple – PMH, other systemic lesions, appropriateness of specialist MDT referral if presumed / proven metastasis – not a focus of this discussion, but still part of the remit of neuro-oncology services, and share common presentation and referral routes

The Patient Journey

The Patient Journey

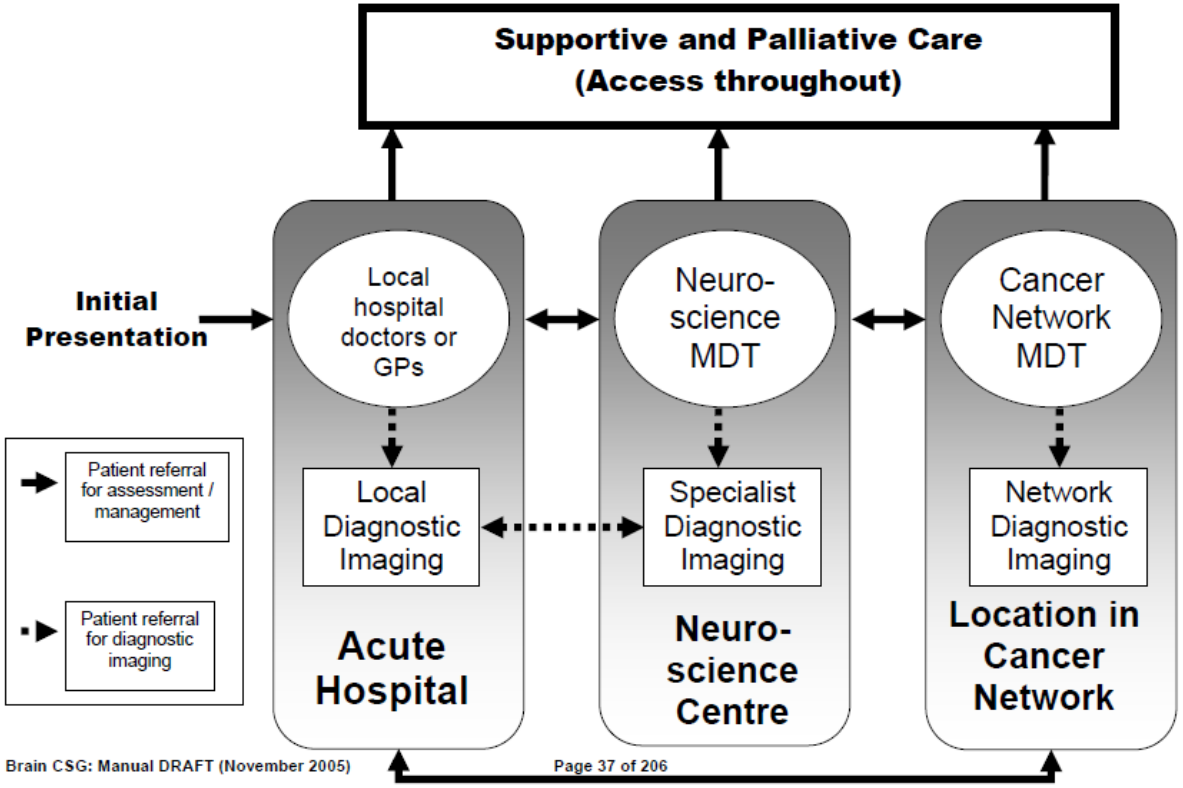
- Various mosaic patterns weave through the pathway:

The Patient Journey

- Various mosaic patterns weave through the pathway, How to get from A to B
- Presentation
- Awareness
- Scanning
- MDT – when, how often?
- Access to specialist services – neurology, psychology, CNS, etc – who, when, how?

NICE summary:

Figure 4: Brain and Other CNS Tumours Patient Pathway



The Patient Journey

- Presentation
- Multiple generic symptoms – headache, tiredness, lassitude, depression, TIA, seizure
- Commonest age of presentation - >50s
- Few prompt urgent investigation
- Many are very non-specific – only realisation that more serious aetiology with persistence or appearance of clinical signs
- Few headaches are textbook

The Patient Journey

- Headache:
- Stress, trauma, drugs, migraine, wrong glasses, tiredness, arthritis in neck, psychiatric/psychological (secondary gain), etc etc
- And – tumour – raised intracranial pressure – bending down, coughing, mornings, nausea, blurred vision

The Patient Journey

Distressing delay in achieving diagnostic scan.

- Little consolation that this rarely affects overall prognosis or therapy
- Raise awareness of clinical warning signs – check optic discs for papilloedema, synchronous symptoms, unusual for individual
- Cf lung, bowel, melanoma, etc etc

The Patient Journey

- High risk populations - Smokers; moles changing (CNS - ?)
- Warning symptoms – persistent cough; GI bleeding (CNS – headache?)
- Screening – HPV cervix; breast (CNS – mobile phones….?)

- None apply

The Patient Journey

- Additional difficulty:
- Multiple different routes – GP, Stroke unit, general medicine, neurology, psychiatry
- Design of referral model and assessment of timing difficult (again cf lung cancer – GP “suspicious of cancer” – clock starts)

The Patient Journey

- Detecting Cancer Early
- SG initiative – focus on colorectal, breast, lung
- Can we apply in CNS tumours?
- No “at risk” patients, no specific symptoms, no specific group clinicians, low incidence

- Difficult

The Patient Journey

- Final common pathway is to neurosurgery as tissue diagnosis essential (see later!)

- This is where controversy really starts

The Patient Journey

- When is correct time – first abnormal scan, full diagnostic work-up (CT and MR brain, CT chest abdo, +/- PET; bloods including tumour markers; assessment of fitness; optimisation of physical fitness – eg steroids or not)
- When appropriate for input of MDT?
- Which neurosurgeon?
- Which oncologist?
- Which centre?
- Which treatment?

The Patient Journey

- Speed (convenience) vs optimal management

The Patient Journey

Model 1

- Referred to on-call neurosurgery team when scan suggest tumour – advice over telephone on any further appropriate scans, bloods, symptom improvement, steroid therapy before decision to admit for surgery
- Individual neurosurgeon makes decision on appropriateness of degree of surgery
- Referred on when formal pathology available and seen by (local) general oncologist with a “bit of an interest” who reads the journals and speaks to friends and colleagues to keep up-to-date on optimal therapy
- Delivery of XRT and/or chemo with support from oncology centre’s staff (radiographers, chemo nurses, secretarial staff, etc)

The Patient Journey

- Not an acceptable model-of-care
- Quick
- Convenient
- Cheap, low resource
- NICE; QPIs
- MDT

The Patient Journey

- What is MDT and why is it necessary?

The Patient Journey

NICE guidance on brain tumours -

- Many patients are severely disabled by their disease
- Many patients have a poor prognosis
- They present through a variety of specialties
- There are significant differences in the care needs of patients with tumours of different histological types and arising in different parts of the CNS
- Many tumour subtypes are extremely rare
- Many patients experience long term progressive cognitive, physical and emotional problems

Never mind driving, employment, financial issues….

NICE:
What constitutes
Neuro-oncology
MDT

Neurosurgeon(s)	Specialist neurosurgeon who spends at least 50% of their clinical programmed activities in neuro-oncological surgery and are regularly involved in dedicated speciality clinics caring for these patients.
Neuroradiologist(s)	A consultant radiologist in a substantive post with at least 50% of clinical programmed activities spent in the practice of neuroradiology.
Neuropathologist(s)	An accredited pathologist who is registered as a neuropathologist or histopathologist, has specialist expertise in neuro-oncology, and takes part in the national External Quality Assurance (EQA) scheme for neuropathology organised by the British Neuropathological Society.
Neurologist(s)	A consultant neurologist with expertise in neuro-oncology, epilepsy or neuro-rehabilitation
Oncologist(s)	A clinical oncologist with a special interest in tumours of the CNS.
Clinical Nurse Specialist(s)	A nurse with specialist knowledge of CNS tumours and skills in communication as defined by the Manual of Cancer Services.[9]
Palliative care	A healthcare professional (normally a member of the specialist palliative care team) with experience and expertise on the provision of palliative care services for CNS tumour patients.
Neuropsychologist(s)	A clinical neuropsychologist with a special interest in tumours of the CNS
Specialist AHP(s)	Representative(s) of the allied health professionals, including, occupational therapy (OT), physiotherapy, speech and language therapy, dietetics and others as appropriate who have knowledge and experience of dealing with this patient group with responsibility for education and liaison with other local specialist AHPs.
Coordinator(s)	An administrative post responsible for coordinating patient registration with the neuroscience MDT and data collection.
Others as required (extended MDT members)	Representatives from ward nursing, community palliative nursing, psychology/psychiatry, neuropsychiatry and epilepsy nurse specialists.

The Patient Journey

- Generally accepted that every patient with newly diagnosed brain tumour have a right to formal discussion of management at properly constituted Neuro-oncology MDT

The Patient Journey

Model 2

- Suspicion of brain tumour – referral to local neuro-oncology MDT
- Pre-operative discussion - input from specialist neuro-radiology, dedicated neuro-surgeon with specific interest in brain tumours, neuro-oncologist, palliative care consultant and AHPs including CNS.
- Review at appropriate clinic
- Seen pre-op by surgeon and oncologist; optimal surgery +/- intra-operative therapy planned; identification of potential clinical studies
- Support by specialist neuro-oncology / neurosurgery CNS
- Awake craniotomy, intra-operative ultrasound, ALA-guided resection, etc

The Patient Journey

- Surgery
- Discussion as post-op MDT, specialist neuropathology, assessment of extent of resection, further identification of clinical studies
- Optimal management suggested
- Early post-op review by surgeon and oncologist to discuss diagnosis, prognosis and choices for next therapy
- Delivery of state-of-the-art radiotherapy and/or chemo / biological therapies, vaccines.
- Ongoing support from specialist services – CNS, specialist radiographers, palliative care, other AHPs
- Reviewed and supported by neurology services if epileptic

The Patient Journey

- Much slower
- Costly in terms of time and resource
- Achievable with management of resource – lots of time, but limited personnel (against not much time, but lots of people, non-specialists, involved)
- Model currently being delivered in some cancer centres down south
- Support services crucial to optimal delivery, but again, expensive and under review

The Patient Journey

- Any evidence one model is better?
- Essentially overall “no”

The Patient Journey

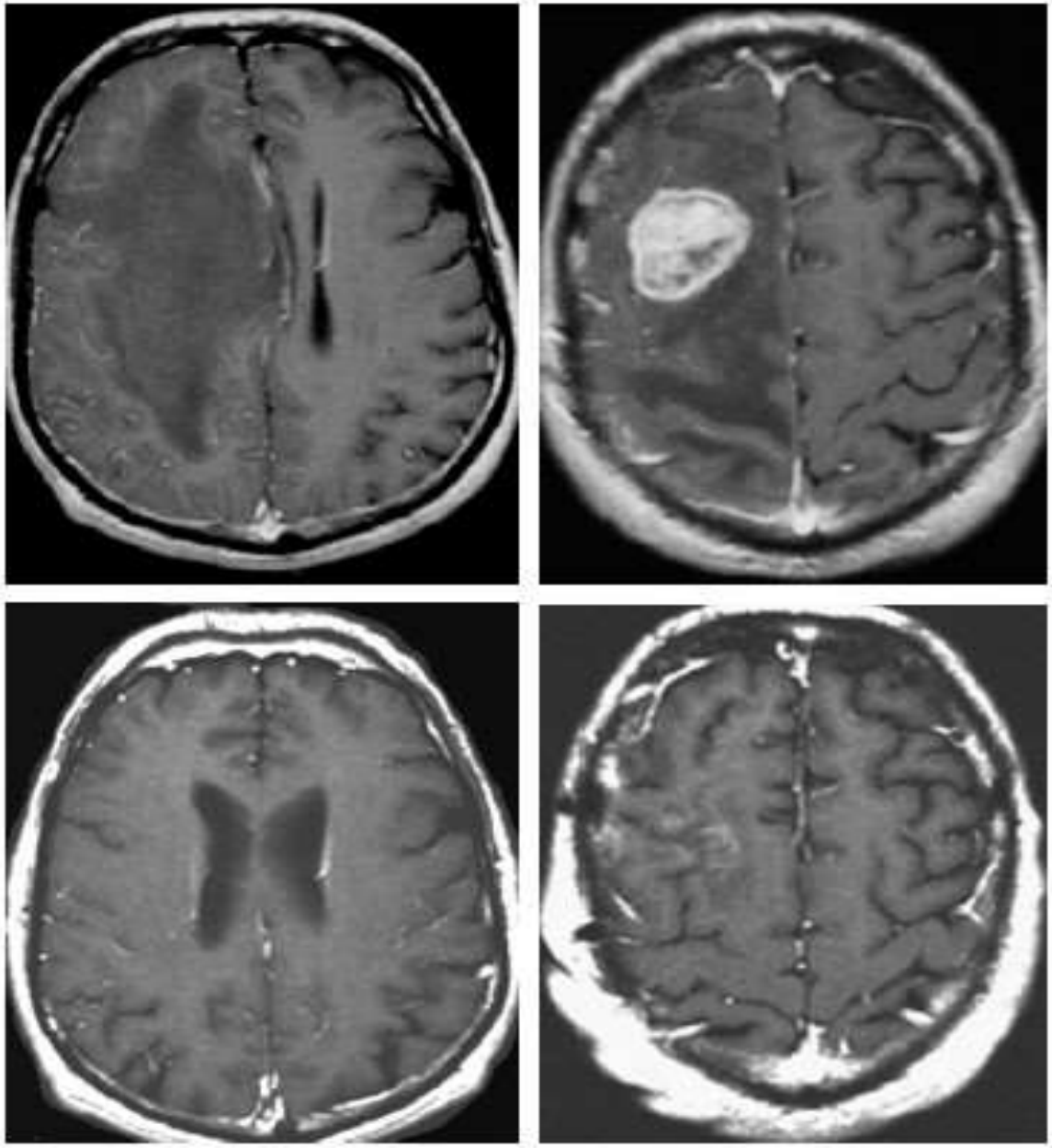
- General principle in medicine, and oncology that specialisation improves outcome
- Multiple studies (eg gastric cancer surgery, rectal cancer surgery, oesophagectomy, etc etc) show less morbidity, better survival in centres and individuals carrying out more specialist procedures
- No specific evidence for brain tumours
- Is brain tumour surgery “specialised” neurosurgery?

The Patient Journey

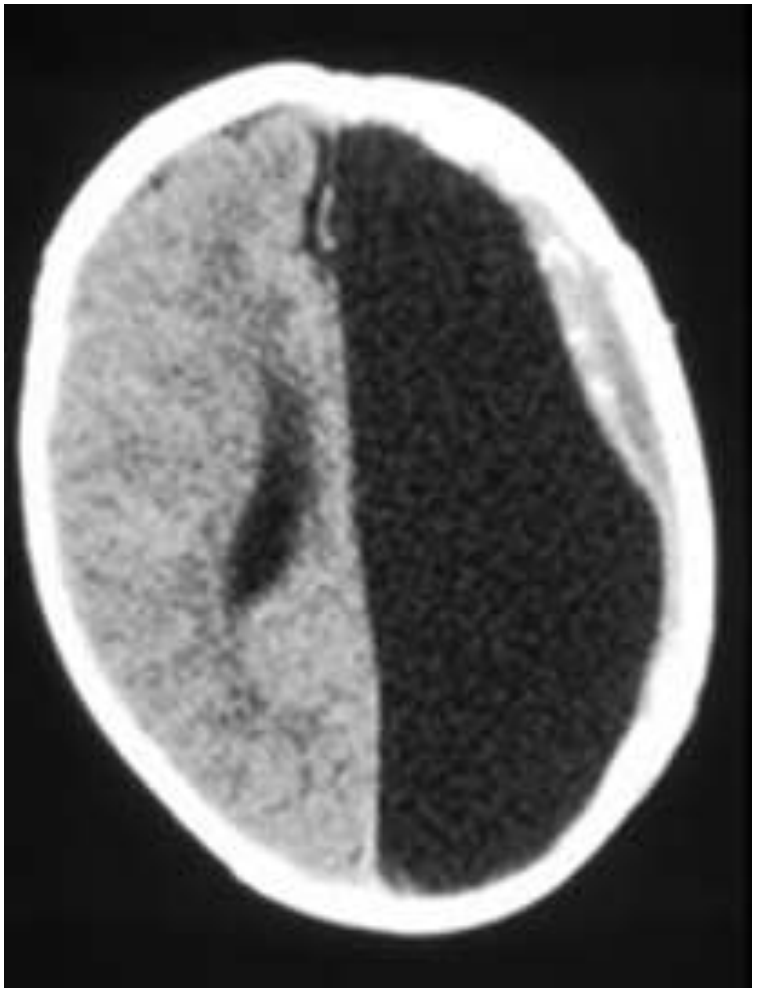
- Q – is this lesion better debulked or not – what additional info would be gained from more tissue and is this helpful – is there a survival advantage – is there a symptom advantage – is radiotherapy / chemotherapy better after extensive surgery – is one of these avoidable if extensive surgery – is there a role for intra-operative therapy – is there a role for functional mapping - is there a role for guidance-surgery (ALA, US) – is there a need to measure degree of resection

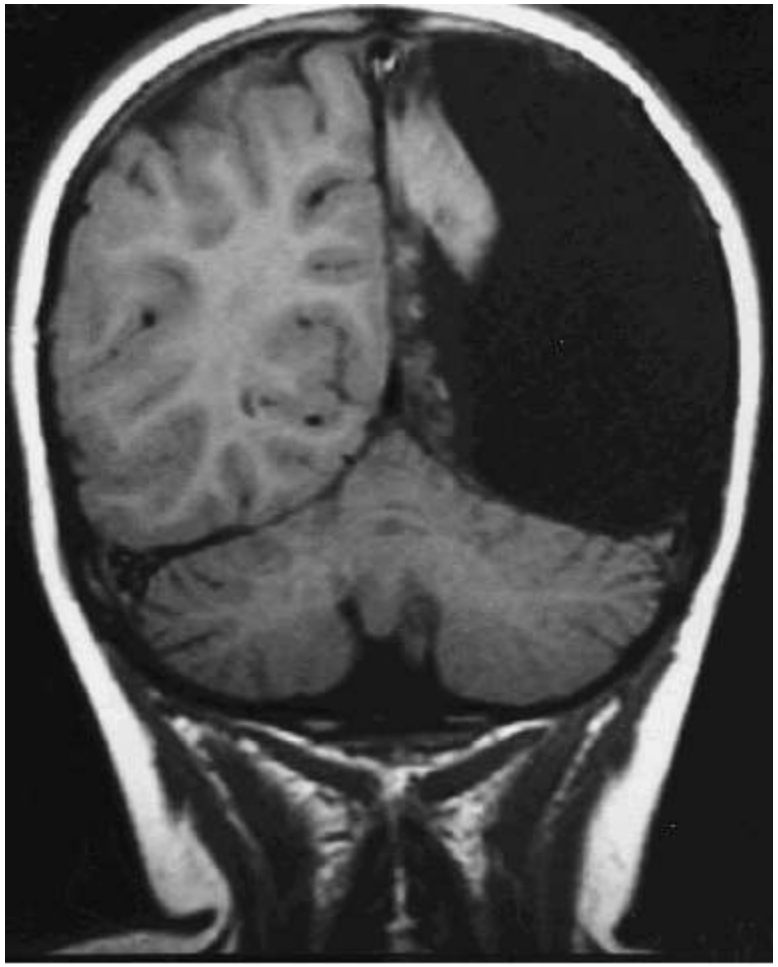
Pre-operative

Post-operative
Fully debulked
Pressure relieved
Ventricles open



Limitations of surgery…….





IT IS NEVER CURATIVE IN GLIOMAS, ESPECIALLY HIGH GRADE DISEASE

The Patient Journey

SUPERCALIFRAGILISTIC HEMOSIDEROSIS: A RARE AND UNUSUAL COMPLICATION THAT REALLY SOUNDS ATROCIOUS. . .

Anatomical Hemispherectomy for Intractable Seizures: Excellent Seizure Control, Low Morbidity and No Superficial Cerebral Haemosiderosis

O'Brien DF, Basu S, Williams DH, May PL

Childs Nerv Syst 2006;22:489–498.

OBJECTIVE: This current study was performed to evaluate whether superficial cerebral hemosiderosis (SCH) is still a complication of modern day anatomical hemispherectomy.

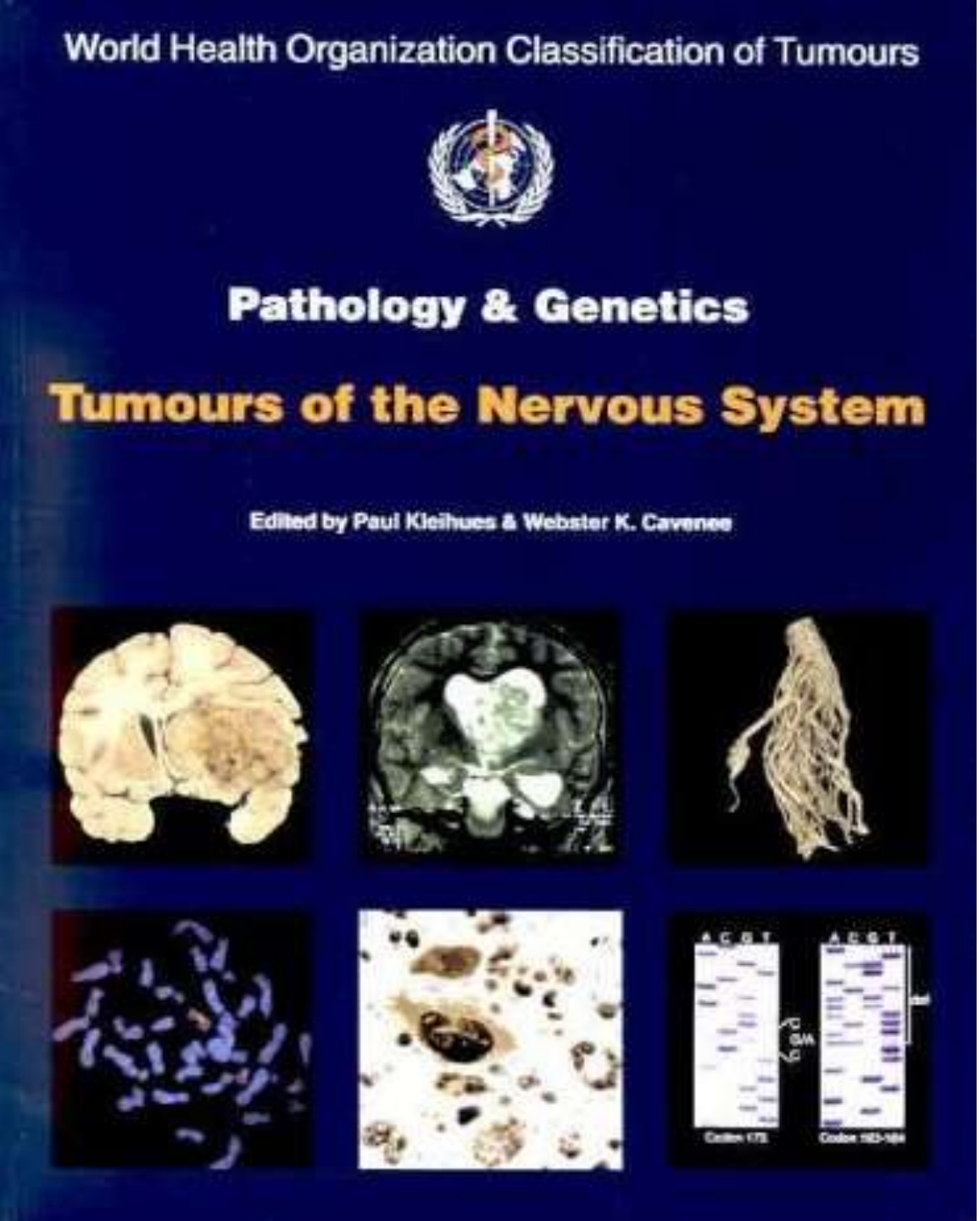
METHODS: We report a 13-year institutional experience with anatomical hemispherectomy for intractable epilepsy. Seizure control at a mean follow-up interval of 7 years was 83%. Though one patient died post-operatively from a nonneurosurgical complication, mortality was otherwise zero and morbidity minimal. The much-described complication of SCH following anatomical hemispherectomy was nonexistent. We explain the history of SCH as a complication of anatomical hemispherectomy, and the measures that are presently taken to prevent it.

CONCLUSIONS: We suggest that the importance of SCH in modern epilepsy surgery is probably over-emphasized.

The Patient Journey

- My answer would be “YES”, this is specialised neurosurgery

- In oncology, increasing complexity of management means unreasonable to expect general knowledge of all cancers; specialisation in 1 or 2 sites recommended by national colleges. QPI (and NICE) state MDT required specialist neuro-oncologist to constitute



- This culminated in 1993 with the publication of the WHO Classification of brain tumours.
- Which has been adopted almost universally as the clinical and research standard and is regularly updated
- Increasing debate as to prioritisation of more complex specialised molecular pathology testing over traditional morphological categorisations

WHO Classification of Tumours of the Nervous System

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Diffuse astrocytoma	9400/3[1]
Fibrillary astrocytoma	9420/3
Protoplasmic astrocytoma	9410/3
Gemistocytic astrocytoma	9411/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Pilocytic astrocytoma	9421/1
Pleomorphic xanthoastrocytoma	9424/3
Subependymal giant cell astrocytoma	9384/1
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Mixed gliomas	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	*9382/3*[2]
Ependymal tumours	
Ependymoma	9391/3
Cellular	*9391/3*
Papillary	9393/3
Clear cell	*9391/3*
Tanycytic	*9391/3*
Anaplastic ependymoma	9392/3
Myxopapillary ependymoma	9394/1
Subependymoma	9383/1
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Choroid plexus carcinoma	9390/3
Glial tumours of uncertain origin	
Astroblastoma	9430/3
Gliomatosis cerebri	9381/3
Chordoid glioma of the 3rd ventricle	*9444/1*

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED). Behaviour is coded /0 for benign tumours, /1 for low or uncertain malignant potential or borderline malignancy, (/2 for *in situ* lesions) and /3 for malignant tumours.

[2] The italicised numbers are provisional codes proposed for the third edition of ICD-O. They should, for the most part, be incorporated into the next edition of ICD-O, but they are subject to change.

Neuronal and mixed neuronal-glial tumours	
Gangliocytoma	9492/0
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	*9493/0*
Desmoplastic infantile astrocytoma / ganglioglioma	*9412/1*
Dysembryoplastic neuroepithelial tumour	*9413/0*
Ganglioglioma	9505/1
Anaplastic ganglioglioma	*9505/3*
Central neurocytoma	*9506/1*
Cerebellar liponeurocytoma	*9506/1*
Paraganglioma of the filum terminale	8680/1
Neuroblastic tumours	
Olfactory neuroblastoma (Aesthesioneuroblastoma)	9522/3
Olfactory neuroepithelioma	9523/3
Neuroblastomas of the adrenal gland and sympathetic nervous system	9500/3
Pineal parenchymal tumours	
Pineocytoma	9361/1
Pineoblastoma	9362/3
Pineal parenchymal tumour of intermediate differentiation	*9362/3*
Embryonal tumours	
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Medulloblastoma	9470/3
Desmoplastic medulloblastoma	9471/3
Large cell medulloblastoma	*9474/3*
Medullomyoblastoma	9472/3
Melanotic medulloblastoma	*9470/3*
Supratentorial primitive neuroectodermal tumour (PNET)	9473/3
Neuroblastoma	9500/3
Ganglioneuroblastoma	9490/3
Atypical teratoid/rhabdoid tumour	9508/3

TUMOURS OF PERIPHERAL NERVES

Schwannoma (Neurilemmoma, Neurinoma)	9560/0
Cellular	*9560/0*
Plexiform	*9560/0*
Melanotic	*9560/0*
Neurofibroma	9540/0
Plexiform	9550/0
Perineurioma	*9571/0*
Intraneural perineurioma	*9571/0*
Soft tissue perineurioma	*9571/0*
Malignant peripheral nerve sheath tumour (MPNST)	*9540/3*
Epithelioid	*9540/3*
MPNST with divergent mesenchymal and / or epithelial differentiation	*9540/3*
Melanotic	*9540/3*
Melanotic psammomatous	*9540/3*

TUMOURS OF THE MENINGES

Tumours of meningothelial cells	
Meningioma	9530/0
Meningothelial	9531/0
Fibrous (fibroblastic)	9532/0
Transitional (mixed)	9537/0
Psammomatous	9533/0
Angiomatous	9534/0
Microcystic	*9530/0*
Secretory	*9530/0*
Lymphoplasmacyte-rich	*9530/0*
Metaplastic	*9530/0*
Clear cell	*9538/1*
Chordoid	*9538/1*
Atypical	*9539/1*
Papillary	*9538/3*
Rhabdoid	*9538/3*
Anaplastic meningioma	9530/3
Mesenchymal, non-meningothelial tumours	
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma (intracranial)	8850/3
Solitary fibrous tumour	*8815/0*
Fibrosarcoma	8810/3
Malignant fibrous histiocytoma	8830/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyoma	8900/0
Rhabdomyosarcoma	8900/3
Chondroma	9220/0
Chondrosarcoma	9220/3
Osteoma	9180/0
Osteosarcoma	9180/3
Osteochondroma	9210/0
Haemangioma	9120/0
Epithelioid haemangioendothelioma	9133/1
Haemangiopericytoma	9150/1
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Primary melanocytic lesions	
Diffuse melanocytosis	*8728/0*
Melanocytoma	*8728/1*
Malignant melanoma	8720/3
Meningeal melanomatosis	*8728/3*
Tumours of uncertain histogenesis	
Haemangioblastoma	9161/1

LYMPHOMAS AND HAEMOPOIETIC NEOPLASMS

Malignant lymphomas	9590/3
Plasmacytoma	9731/3
Granulocytic sarcoma	9930/3

GERM CELL TUMOURS

Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumour	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature	9080/0
Immature	9080/3
Teratoma with malignant transformation	9084/3
Mixed germ cell tumours	9085/3

TUMOURS OF THE SELLAR REGION

Craniopharyngioma	9350/1
Adamantinomatous	*9351/1*
Papillary	*9352/1*
Granular cell tumour	*9582/0*

METASTATIC TUMOURS

TUMOURS OF NEUROEPITHELIAL TISSUE

Astrocytic tumours	
Diffuse astrocytoma	9400/3[1]
Fibrillary astrocytoma	9420/3
Protoplasmic astrocytoma	9410/3
Gemistocytic astrocytoma	9411/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Pilocytic astrocytoma	9421/1
Pleomorphic xanthoastrocytoma	9424/3
Subependymal giant cell astrocytoma	9384/1
Oligodendroglial tumours	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Mixed gliomas	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	*9382/3*[2]
Ependymal tumours	
Ependymoma	9391/3
Cellular	*9391/3*
Papillary	9393/3
Clear cell	*9391/3*
Tanycytic	*9391/3*
Anaplastic ependymoma	9392/3
Myxopapillary ependymoma	9394/1
Subependymoma	9383/1

- This section of the list accounts for majority primary adult brain tumours
- Rest may be individually very rare, but as a group, maybe 20-30%
- Keeping up to date with management, eg SEGA and everolimus

The Patient Journey

- CNS – roles to be discussed, but evidence difficult to gather; much of work is not easily measurable
- Clinical trials – increasingly complex to set up and run, large support network required
- Dedicated Neurology input – rare species in UK. Need to try and raise awareness
- State-of-the-art treatment – some evidence

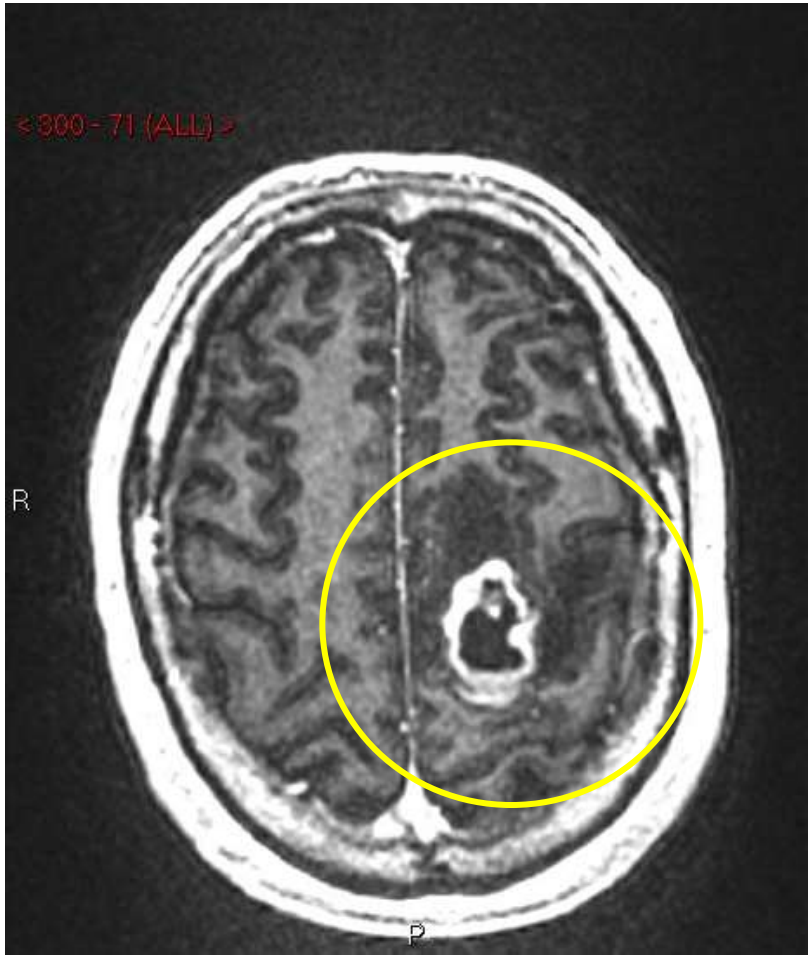
The Patient Journey

- Radiotherapy
- 1970s – survival advantage demonstrated for XRT in glioma
- Dose escalation beyond 60Gy of no benefit – increased side effects / toxicity but no improved survival
- Increasing evidence of role of long-term neuro-cognitive effects of XRT

The Patient Journey

- Volume of brain, dose per fraction, total dose
- Initial technique was whole brain
- Follow-up studies showed vast majority recur within 2-3cm of index site

The Patient Journey



So don’t need to treat whole brain, only region round index lesion

Modern radiotherapy techniques allow this with increasing sparing of normal brain

The Patient Journey

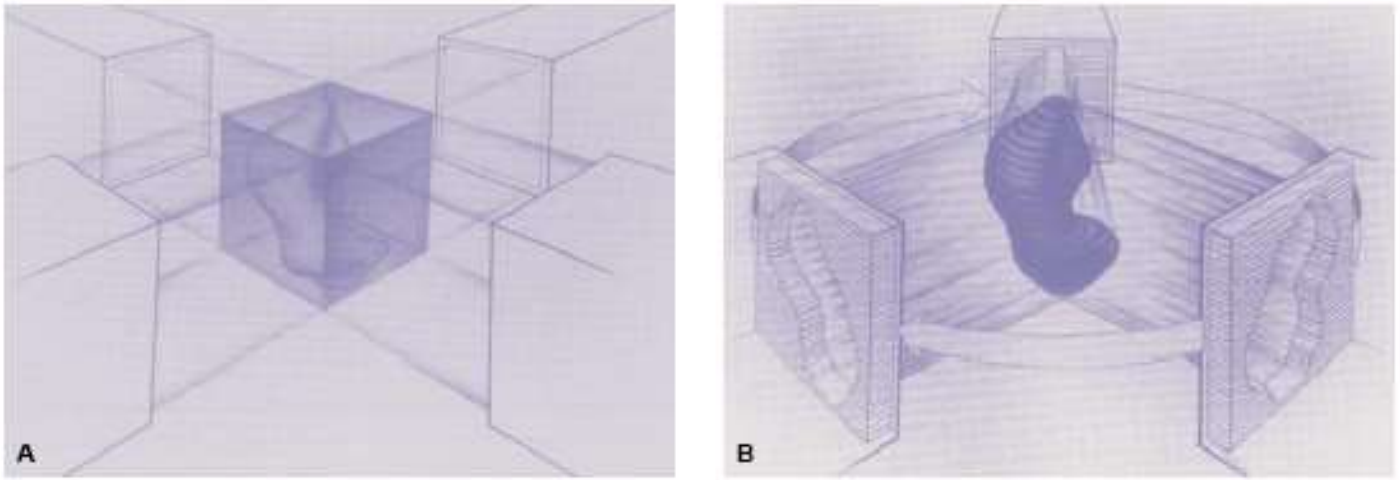
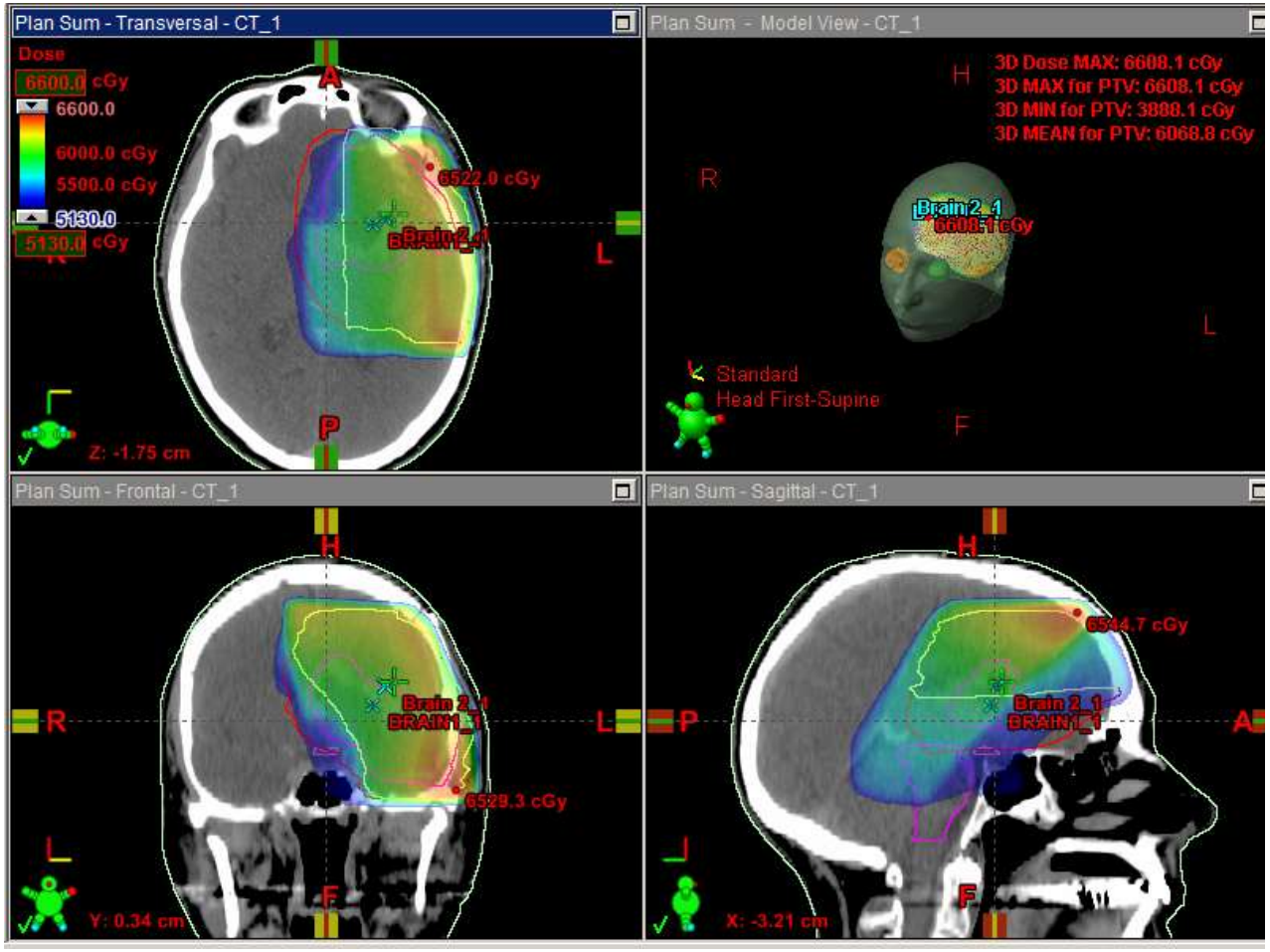


Figure 7–1. *A*, An illustration of nonconformal radiation therapy. Use of a few simply shaped rectangular radiation fields produce a treatment volume that is cuboidal and includes a considerable amount of normal tissue. *B*, An illustration of conformal radiation therapy. Multileaf collimation of multiple or moving radiation beams produces a shape that conforms closely to the "beam's-eye view" configuration of the tumor. Intensity modulation can alter radiation fluency within the beam's-eye view field shape to increase conformality even further. (Reproduced with permission from Lichter AS, Fraass BA, McShan DL, et al. Recent advances in radiotherapy treatment planning. Oncology 1998;2:43–57.)

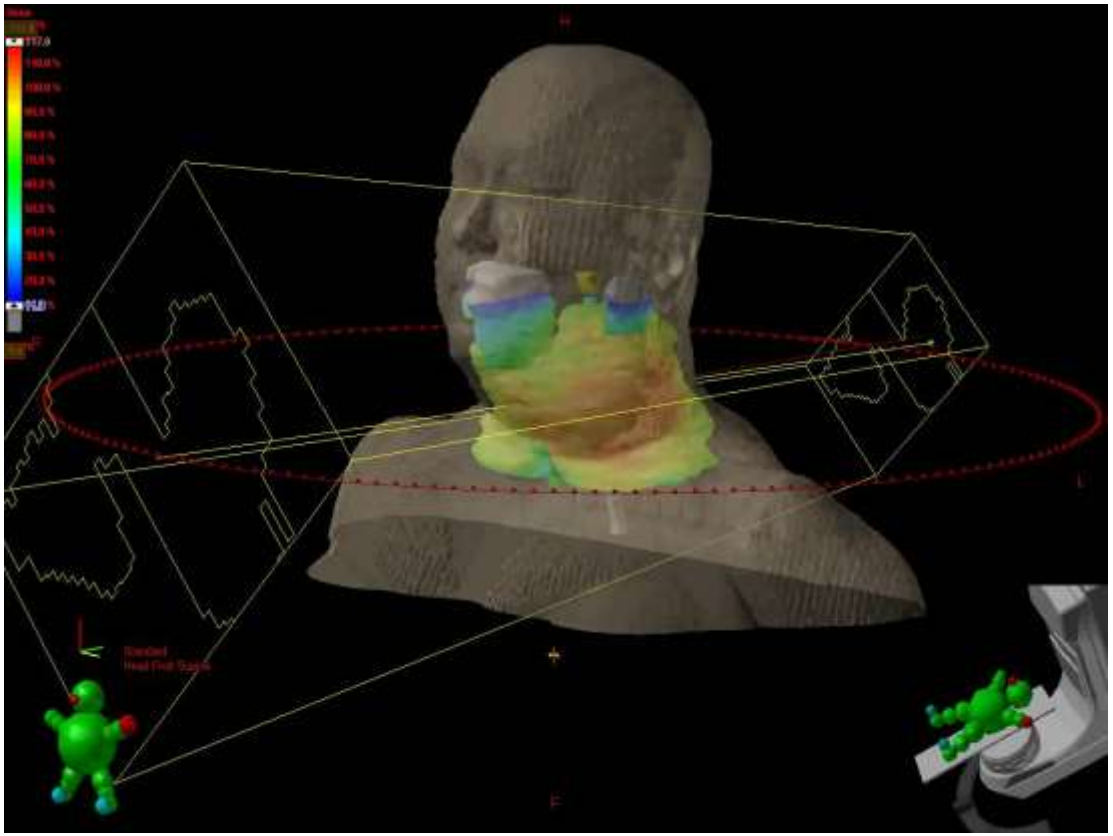
The basis for conformal planning – radiotherapy portal shaped to match the tumour from that specific perspective, shielding off normal tissues. By overlapping multiple beams, also cuts down on dose to normal tissue by ensuring only the tumour sees the full dose from intersection of all beams.

The Patient Journey



Conformal XRT
Dose distribution

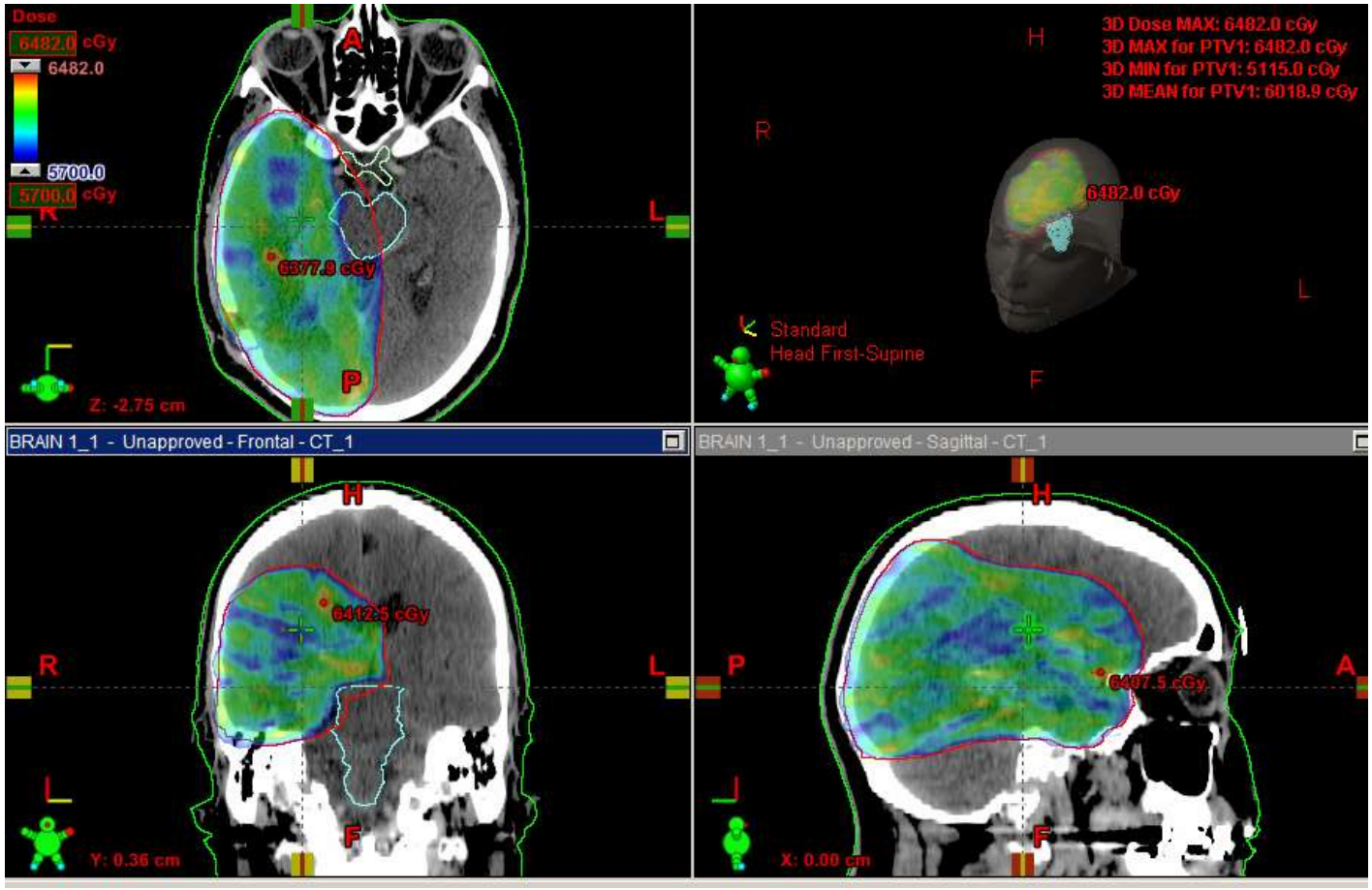
The Patient Journey



Most modern technique – Everything moves!
Allows complex shaping of high dose region and sparing of normal tissues (dose painting)

VMAT
Velocity modulated arc therapy

The Patient Journey

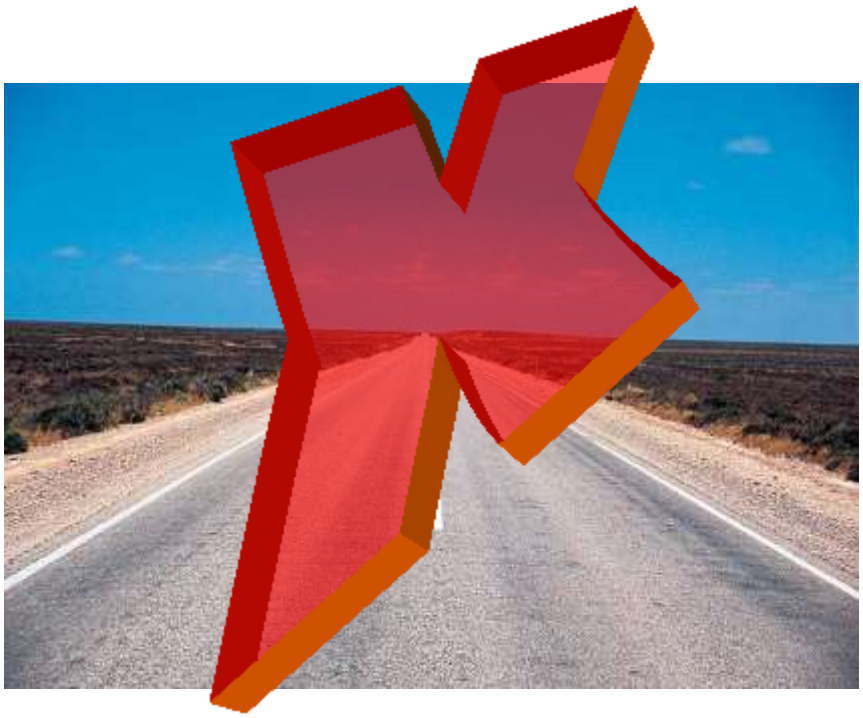


VMAT dose distribution

The Patient Journey

- Again, more resource, and slower - to ensure done right
- No specific evidence better than old techniques
- First principles

The Patient Journey



The Patient Journey

- Happy medium
- Optimal management in timely manner