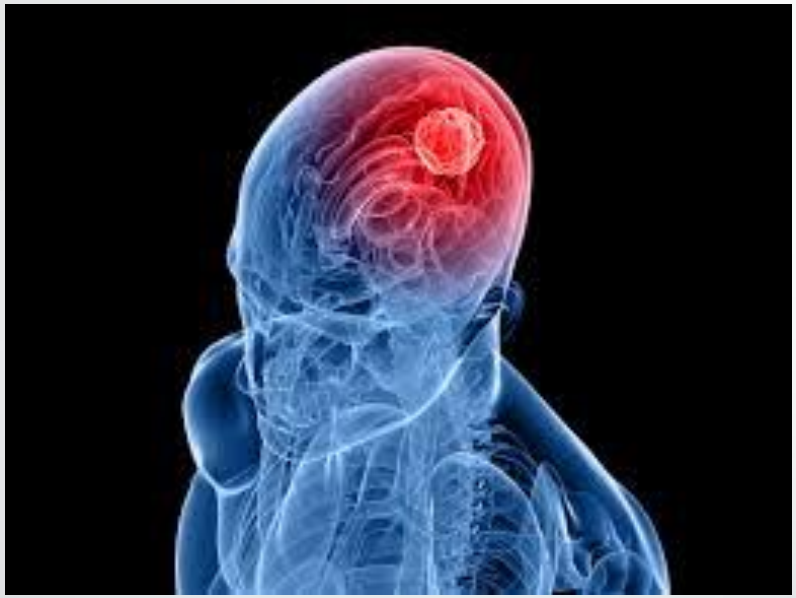
Current Neurosurgical Approaches for Brain Tumour Patients and Future Trends in Neurosurgery



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IBTA
Sitges
2015

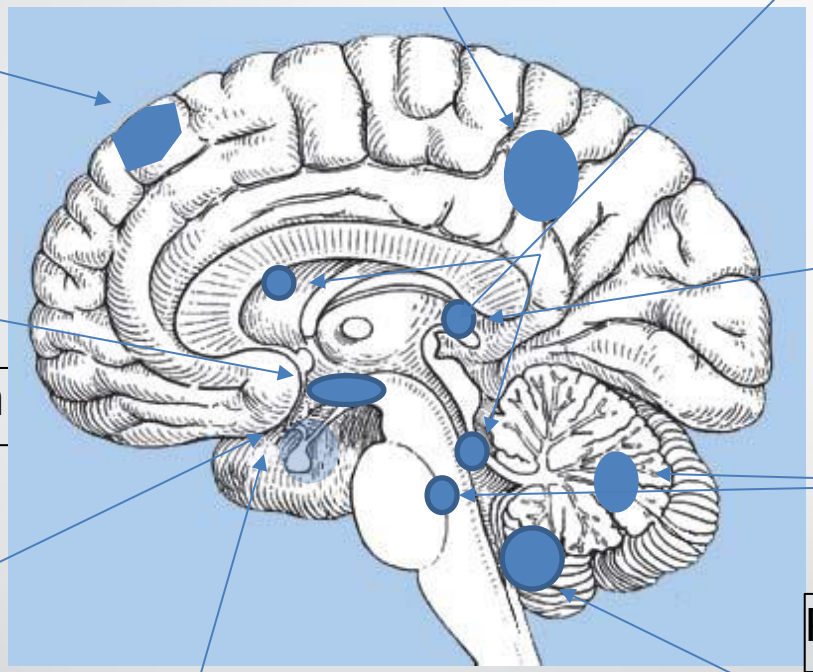
Cerebral Hemispheres

Intrinsic:
Astrocytoma
Glioblastoma
Ganglioglioma
Lymphoma
Metastasis

Extrinsic:
Meningioma
Cysts-(Dermoid
Arachnoid)

Ventricular System

Colloid cyst
Choroid plexus papilloma
Ependymoma
Germinoma
Teratoma
Meningioma
Pineo-cytoma/blastoma
astrocytoma



Hypothalamus

astrocytoma

Pineal region

Sellar/suprasellar Region

Pituitary adenoma
Craniopharyngioma
Meningioma
Optic nerve glioma
Epidermoid/dermoid

Intrinsic:
Metastasis
Haemangioblastoma
Medulloblastoma
Astrocytoma
(cerebellum /brainstem)

Posterior Fossa

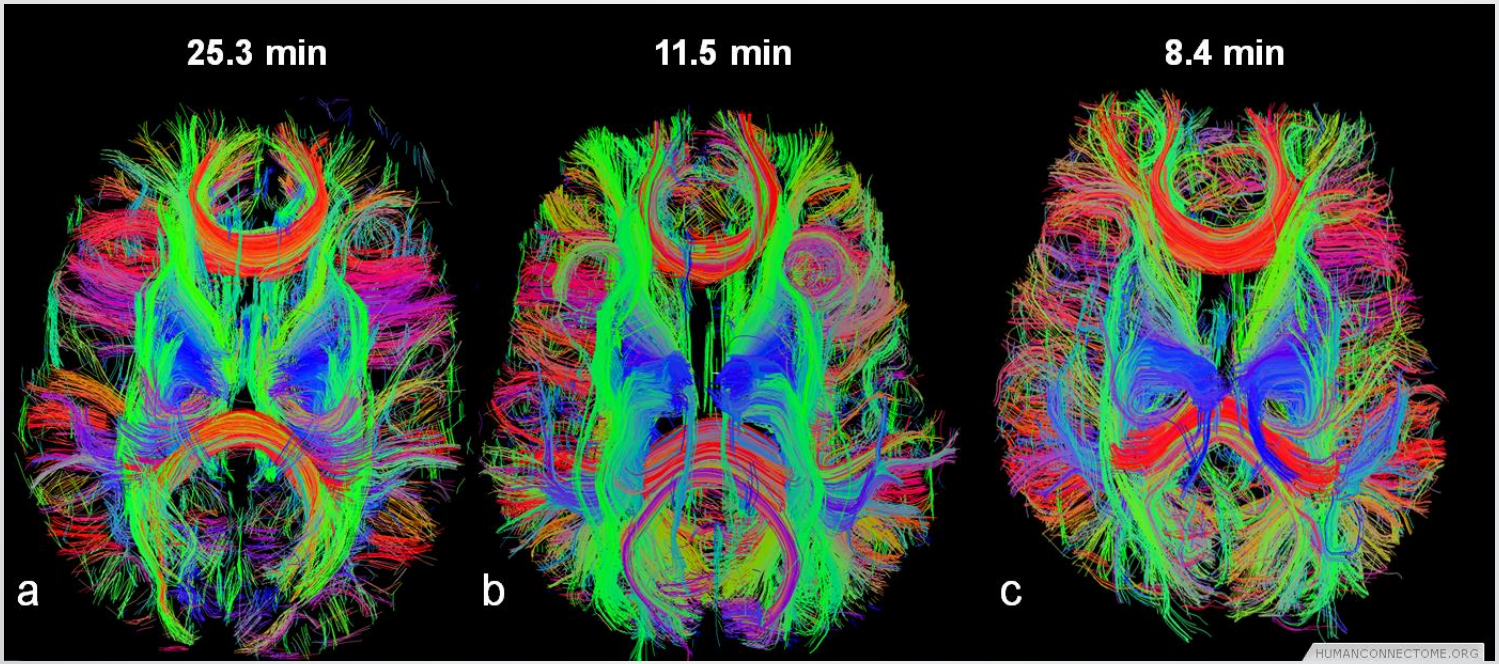
Skull Base and Sinuses

Carcinoma (nasopharyngeal, sinuses, ear)
Chordoma
Glomus jugulare tumour
Osteoma> mucocoele
aesthenioneuroblastoma

Extrinsic:
Schwannoma
Meningioma
epidermoid/dermoid
Arachnoid cyst
Metastasis

Tumours can cause many local effects depending the structures close-by

Connections

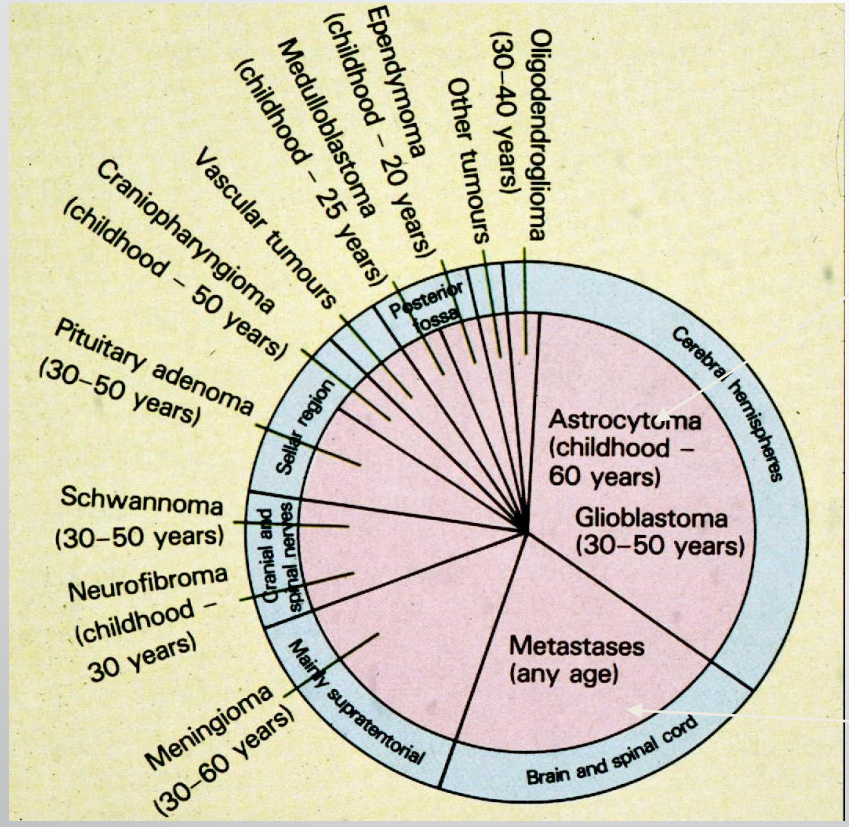


The connections between different areas of the brain form complex networks associated with the higher functions of the mind

Damage to the connections is at least as harmful to neural networking as damage to eloquent sites

Relative Neurosurgical Activity

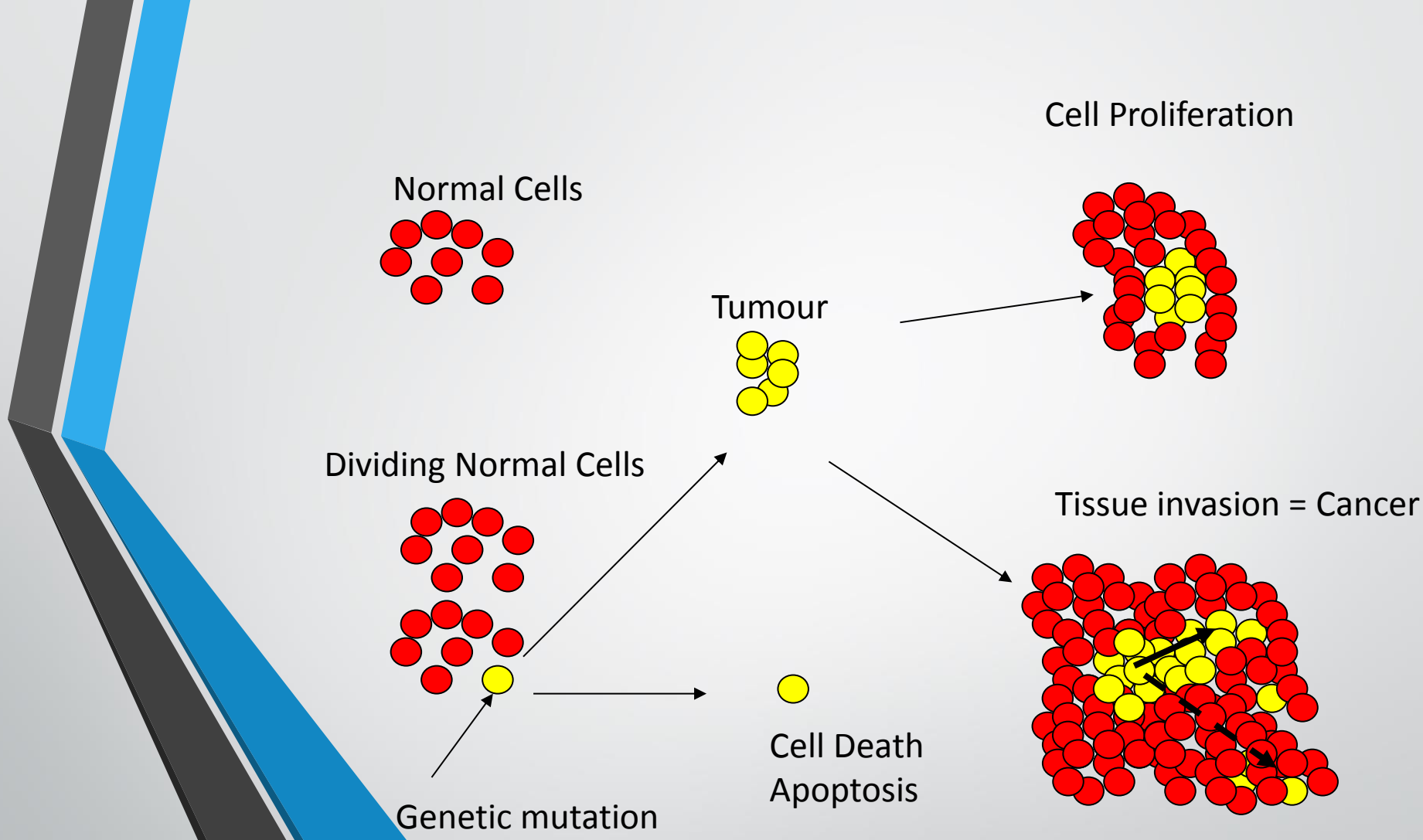
Incidence 16/100,000
8/100,000 are malignant - incidence is increasing!



Glioblastoma	Gd IV
Anaplastic Astrocytoma	Gd III
Astrocytoma	Gd II
Pilocytic Astrocytoma	Gd I

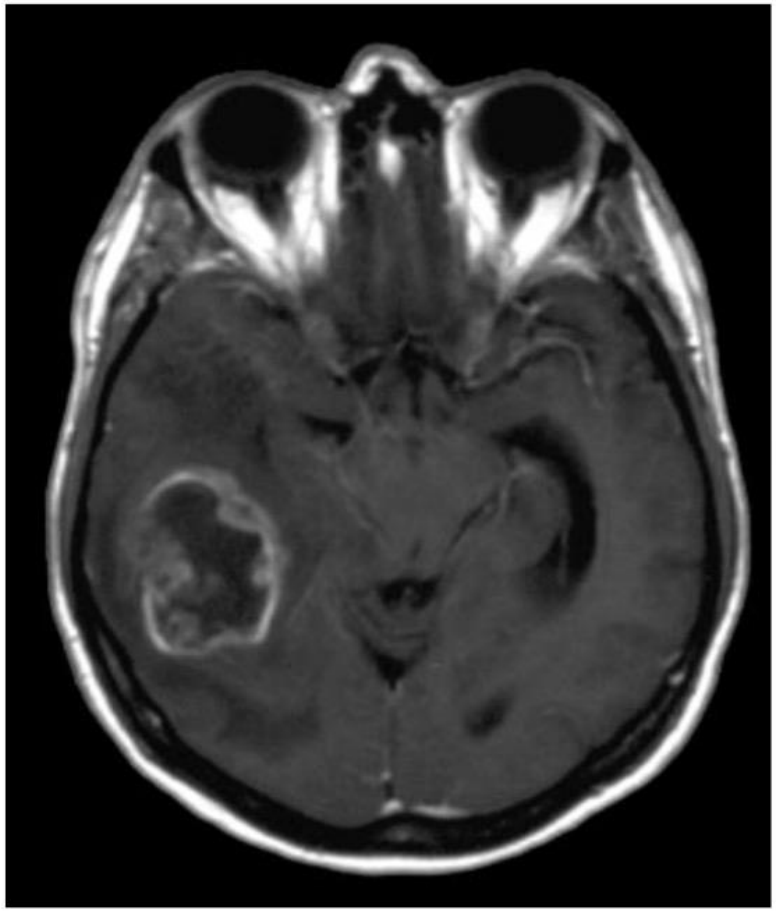
Primary CNS Lymphoma - also increasing!

Lung
Breast
Thyroid
Kidney
Melanoma

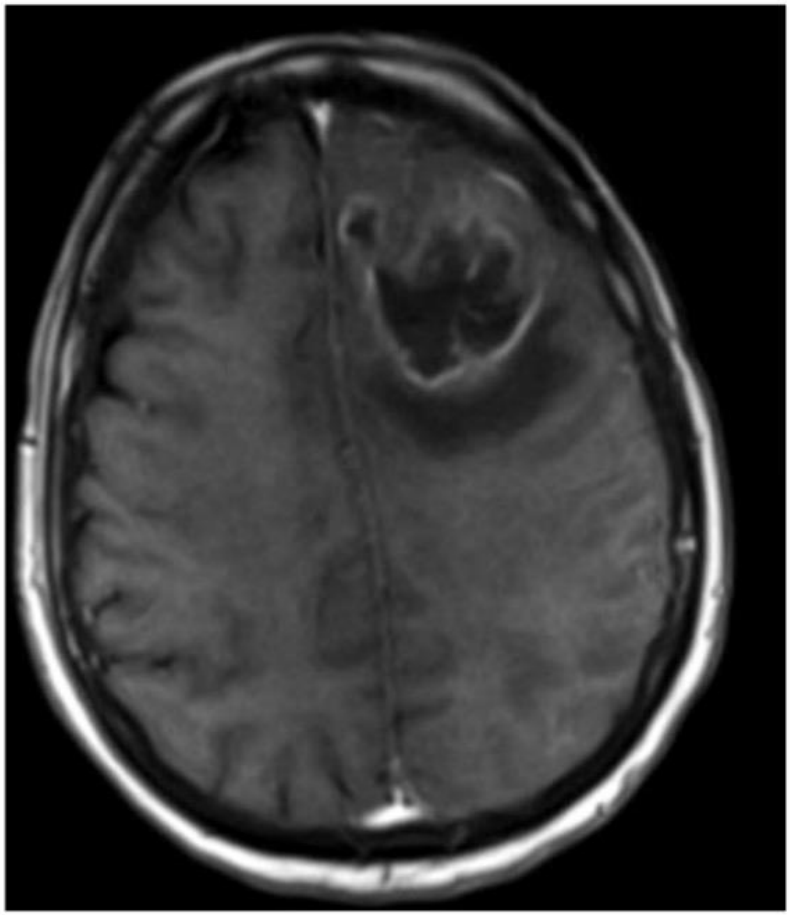


Brain Tumours may grow locally (focal) or spread/invade (diffuse) or both

Three Features of History: Seizures, Focal Symptoms, …Headaches



Short term Memory loss
Left visual Field Loss
Left sensory/motor changes



Personality Change
Expressive Dysphasia
Right sided motor changes

Aims of Surgery in Brain Tumours

	Does What?
1. Biopsy	1. Pathology , Prognosis, Predict treatment response
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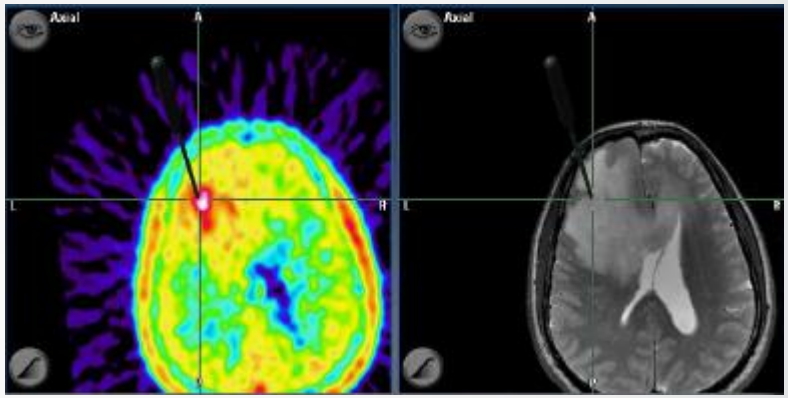
3. Reduction of tumour mass - Enhance adjuvant therapy - Reduce Hypoxia	3. Improves response to radiation and chemotherapy
4. Prolongation of survival?	4. Makes patient live longer?
5. Introduction of Novel Treatments - Drugs - Gene Therapy - Immunotherapy	5. Access to New Treatments

Obtaining a Tumour Biopsy

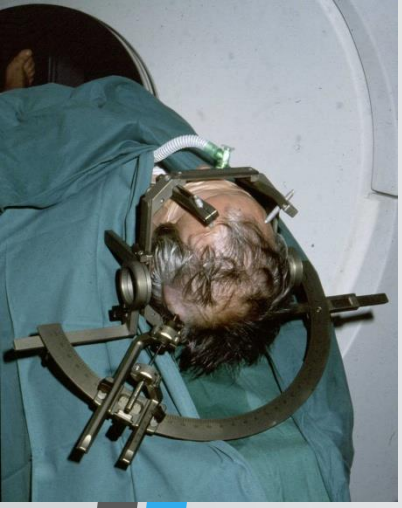
- Stereotactic Biopsy
- Surgical resection



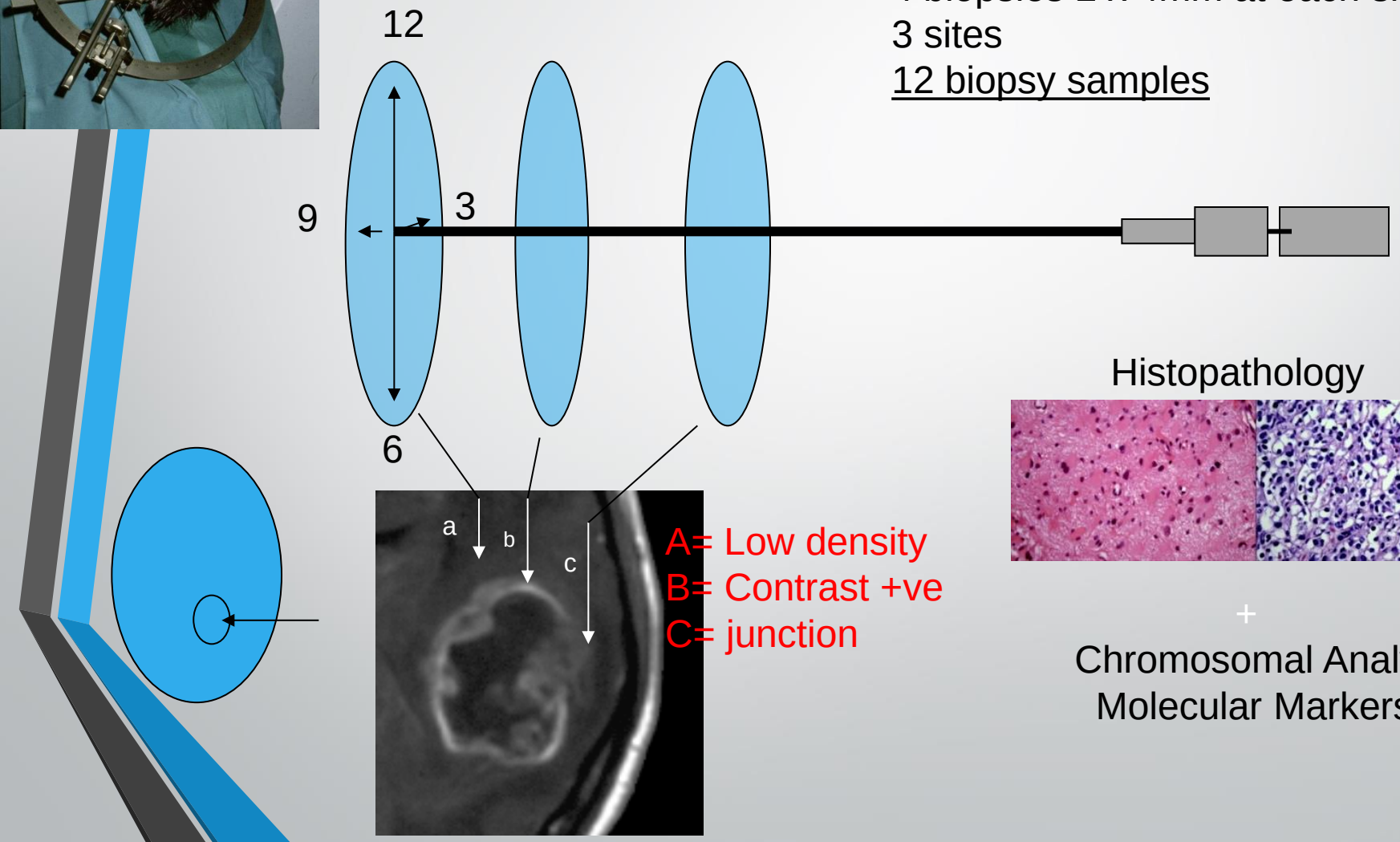
- Peroperative frozen section increases successful diagnostic yield
- Imaging (MRI/PET) Hotspots can help direct the site for best biopsy
- Multiple biopsies allow coverage and definition tumour heterogeneity
- Biobanking of tumour = Tumour Samples +Blood Samples

Tumour/Abnormal DNA vs Patients Normal DNA

Stereotactic Bx Sampling



4 biopsies 2 x 4mm at each site
3 sites
<u>12 biopsy samples</u>



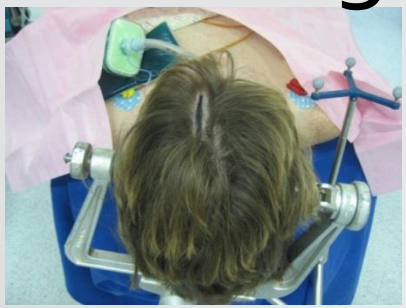
A= Low density
B= Contrast +ve
C= junction

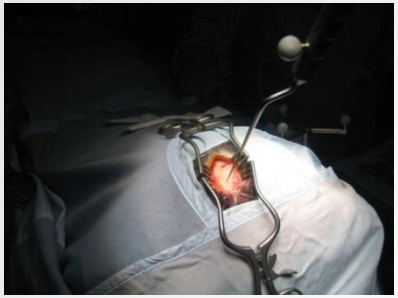
Histopathology

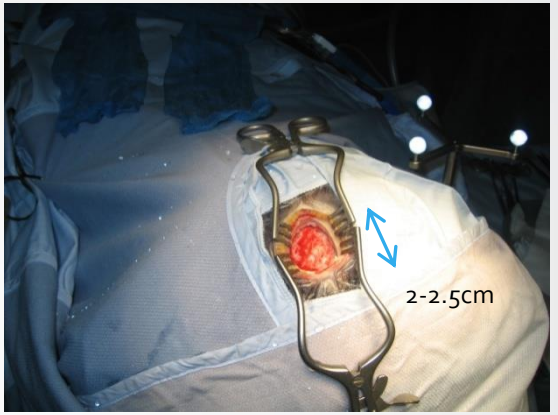
+

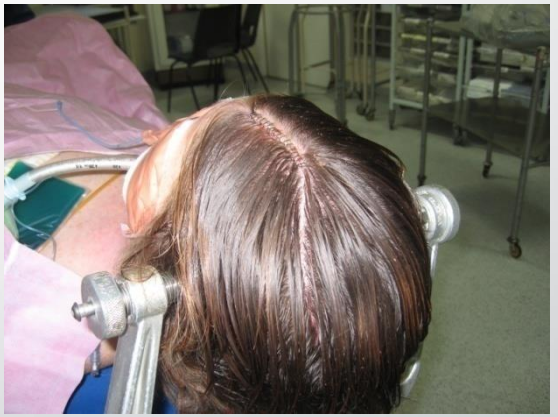
Chromosomal Analysis
Molecular Markers

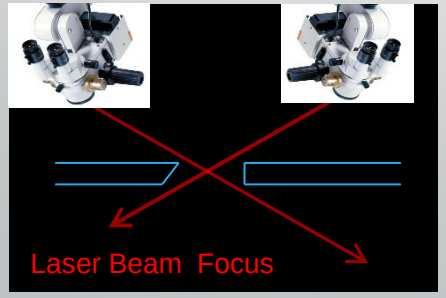
Image Directed Surgery







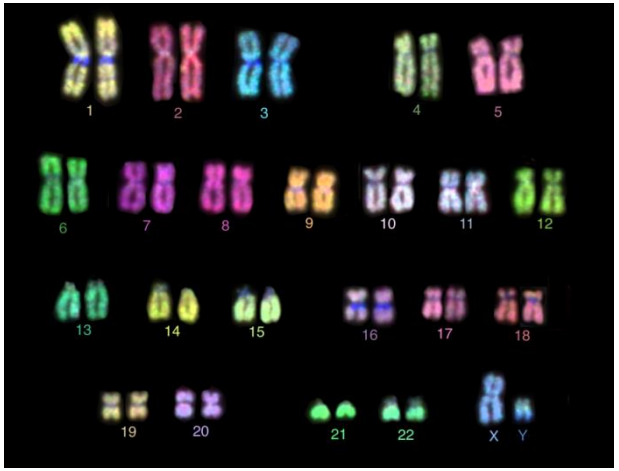




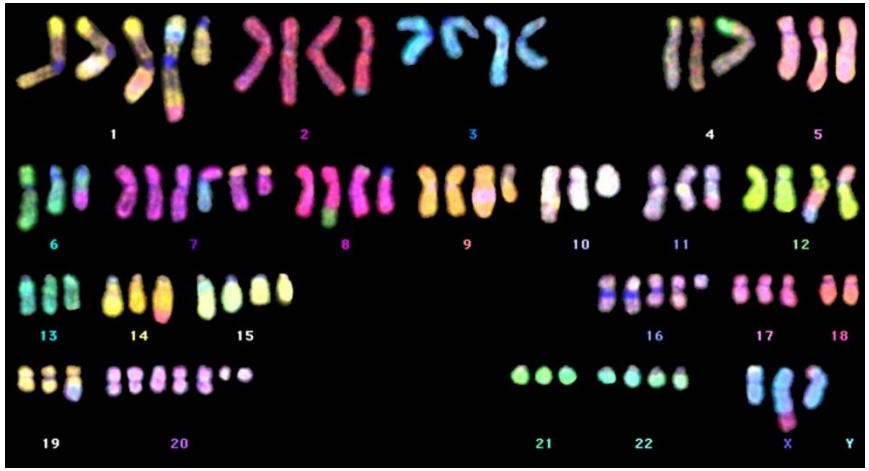
Minimal Disturbance / Microscope
Precise access to tumours
Rapid access, and closure
'keyhole' surgery?

Karyotypes

Normal male



Glioblastoma multiforme



Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in *PDGFRA*, *IDH1*, *EGFR*, and *NF1*

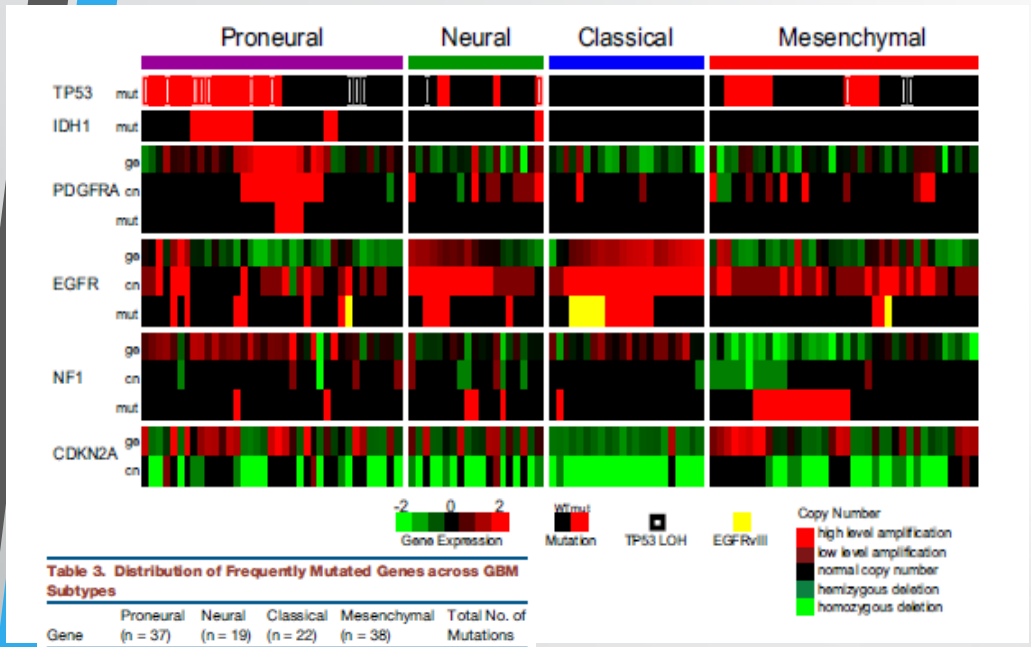
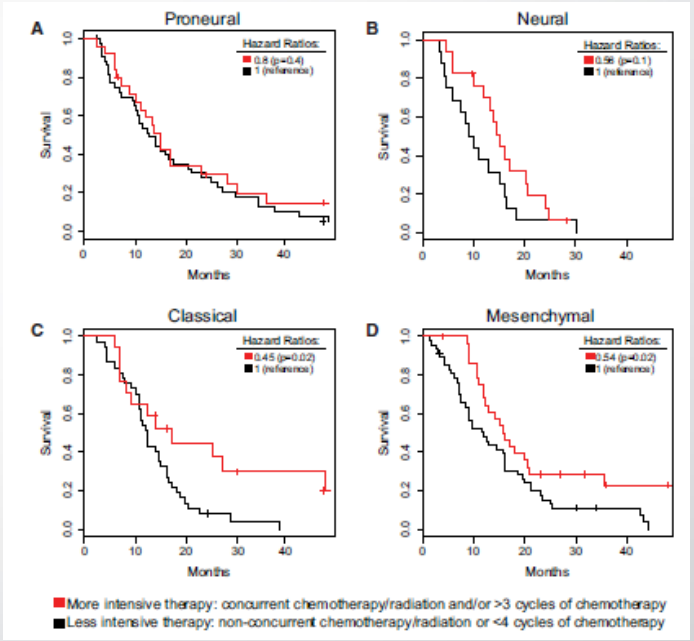


Table 3. Distribution of Frequently Mutated Genes across GBM Subtypes

Gene	Proneural (n = 37)	Neural (n = 19)	Classical (n = 22)	Mesenchymal (n = 38)	Total No. of Mutations
TP53	**20 (54%)**	4 (21%)	**0 (0%)**	12 (32%)	36
PTEN	6 (16%)	4 (21%)	5 (23%)	12 (32%)	27
NF1	2 (5%)	3 (16%)	1 (5%)	**14 (37%)**	20
EGFR	6 (16%)	5 (26%)	7 (32%)	2 (5%)	20
IDH1	**11 (30%)***	1 (5%)	0 (0%)	0 (0%)	12
PIK3R1	7 (19%)	2 (11%)	1 (5%)	0 (0%)	10
RB1	1 (3%)	1 (5%)	0 (0%)	5 (13%)	7
ERBB2	2 (5%)	3 (16%)	1 (5%)	1 (3%)	7
EGFRvIII	1 (3%)	0 (0%)	5 (23%)	1 (3%)	7
PIK3CA	3 (8%)	1 (5%)	1 (5%)	1 (3%)	6
PDGFRA	4 (11%)	0 (0%)	0 (0%)	0 (0%)	4

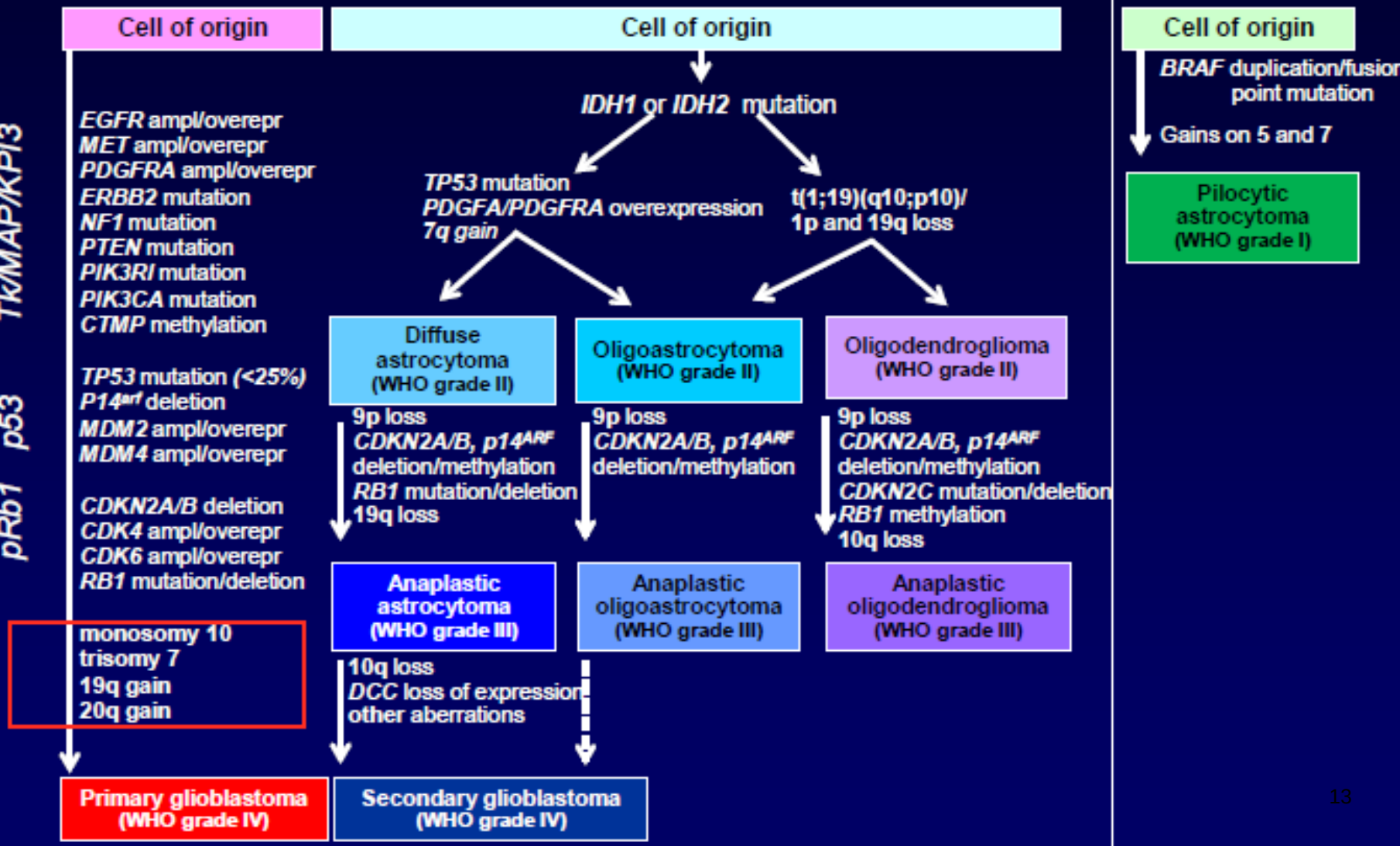
Significance of the difference in number of events between subtypes and remainder of the subtypes was determined using a two-sided Fisher's exact test, corrected for multiple testing using a Familywise Error Rate. Bold type indicates p values significant at an 0.1 level. Also see Figure S5 and Tables S2, S4, and S6.

*p value significant at 0.01 level.



Cancer Cell 17, 98–110, January 19, 2010

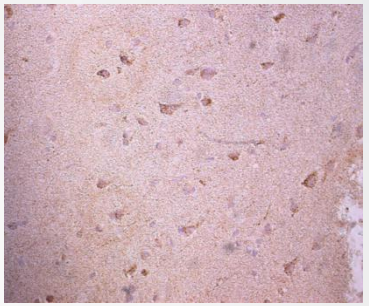
Summary of Most Frequent Alterations in Astrocytic, Oligodendroglial, and Oligoastrocytic Gliomas



Riemenschneider MJ, et al. *Acta Neuropathol*. 2010;120(5):567-584.

Genetics and Biomarkers

Diagnostic: classify tumour – especially LGG
Prognostic: provide prognostic information
Predictive : choose treatment strategies



- 1p19q-Deletion associated with better prognosis AnO 7y vs 2y without
  - Co Deletion prognostic of improved survival OD and OA 12-15 vs 5-8yrs without
  - Co Deletion predictive of AnO and OligoAstro sensitivity to PCV (and temozolomide)
  - Co Deletion predictive of response to chemotherapy in OD NOA-4 2008
- MGMT – methylation leads to loss of repair enzyme MGMT hence increased tumour killing from temozolomide
- IDH1/2 mutations [132] characteristic of LG > HG pathway tumours better prognosis (type II)
- EGFR over expression indicates GBM and hence predictive for Temozolomide regimen

Biomarkers

Prognostic

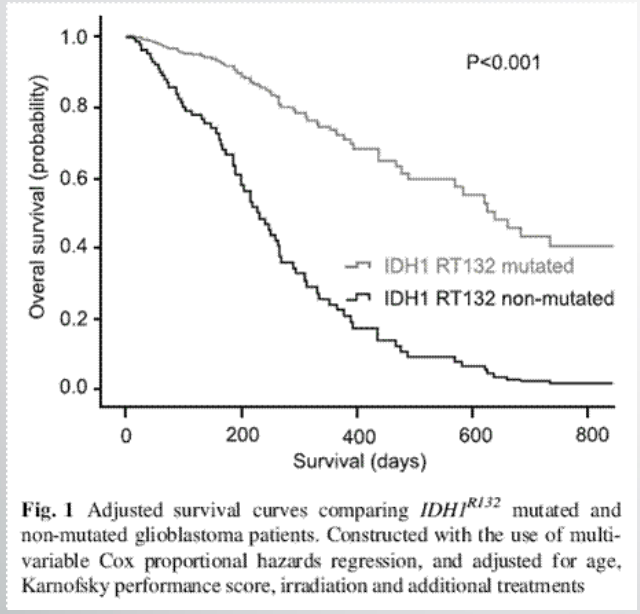
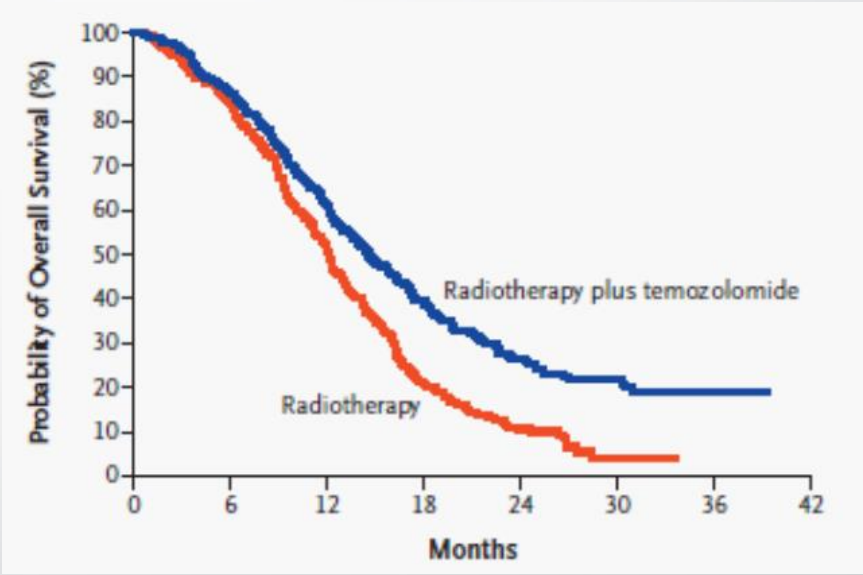


Fig. 1 Adjusted survival curves comparing *IDH1*^{R132} mutated and non-mutated glioblastoma patients. Constructed with the use of multivariable Cox proportional hazards regression, and adjusted for age, Karnofsky performance score, irradiation and additional treatments

IDH 1 Mutation

Predictive



MGMT DNA Repair Deficit

Stupp et al.
N Eng J Med 352 (2005) 987-996

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Tumour Debulking/Resection

Benefits

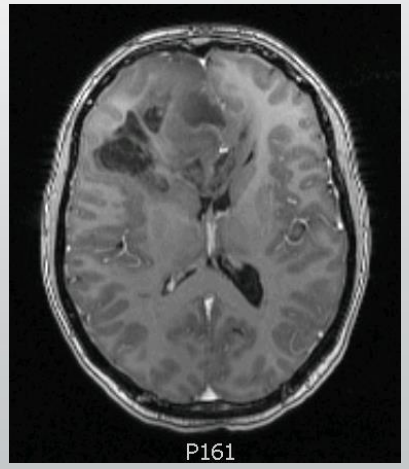
- Reduces tumour mass
- Controls symptoms
- Allows reduction/cessation of steroids
- Improves patient QOL
- Easier passage through radiation
- Control Seizures

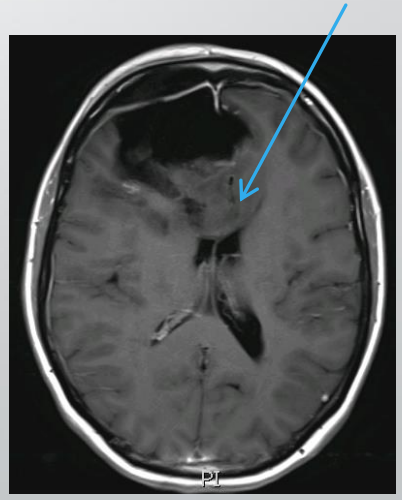
Risks

- Damage/ Deficit
- Time in Hospital
- Seizures ~
- Hair Loss/Disfigurement
- Independence
- Death - <1%

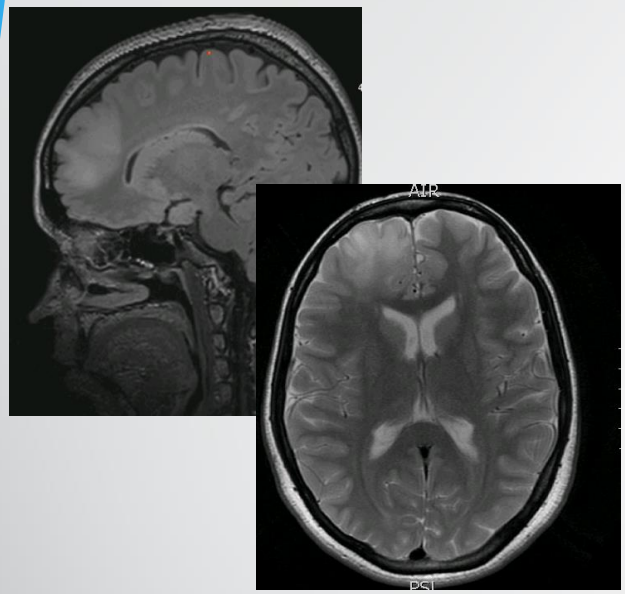
32 yr Male Severe Headache
Confusion
Aggressive behaviour to young family

'Incomplete' removal
"Back to Normal"
Anaplastic Oligodendroglioma
LOH/IDH1 +ve



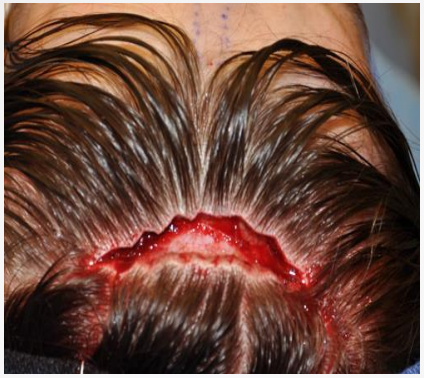


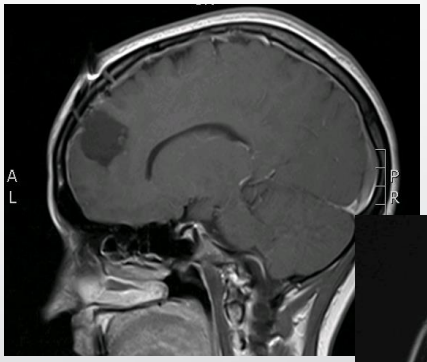
A Patient Acceptable Result



22yr old female
Difficult Seizure Control
Very anxious

MRI and MRS
suggests LGG

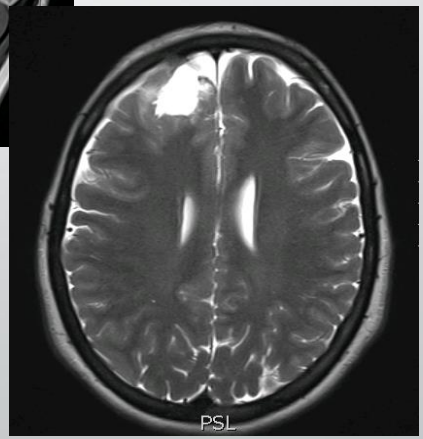




Good Excision
Good control of
Seizures

Cosmetic result
24hr LOS

Path:
IDH1 +ve
Diffuse
Astrocytoma



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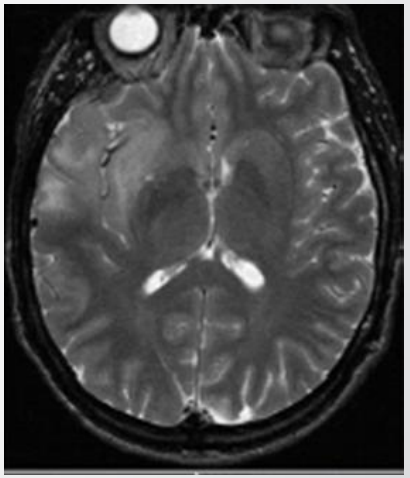
Natural History of Low Grade Gliomas



- 15% of Gliomas
- Pre Malignant not stable tumours.

  -However many are truly indolent.
- Imaging shows progressive growth
- Altered Trajectory of growth may indicate transformation
- All become malignant

Rees J et al . Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation
Eur J Radiol. 2009 Oct;72(1):54-64.

Problems

- Seizures- even minor affect QOL adversly
- Cognitive problems: tumour /seizures/AED's
- Remarkable stability despite morphological change (Duffau – plasticity)
- Determining progression/transformation*
- Individualising Treatment – Long Term Care

*NB: Unexpected large >20% proportion are transforming tumours at presentation !

Current Questions

- Can Infiltrating lesions be removed safely?

  -thus no 'wait and see' vs prolonged morbidity
- Extent of removal determines survival?

  - vs more limited resection +/- RT
- Retaining QOL
- Should all have surgery ? – BAD Low Grades

Guidelines on management of low-grade gliomas: report of an EFNS–EANO* Task Force

European Journal of Neurology 2010, **17:** 1124–1133

Surgical resection represents the first treatment option, with the goal to maximally resect the tumor mass whenever possible, whilst minimizing the post-operative morbidity
(Level B)
Nonetheless, even with intraoperative MRI-guided surgery, total resection is achieved in no more than 36% of patients.

The identification of the eloquent cerebral areas, which have to be preserved during surgery, is performed through pre-operative neuroimaging modalities (functional MRI, fiber tracking) and intraoperative brain mapping techniques (Level B), and awake surgery could improve the results (Level C).

When surgery is not feasible (because of tumor location, extension or comorbidities), a biopsy (either stereotactic or open) should be performed to obtain a histological diagnosis (good practice point).

Cochrane Database Syst Rev. 2013 Apr

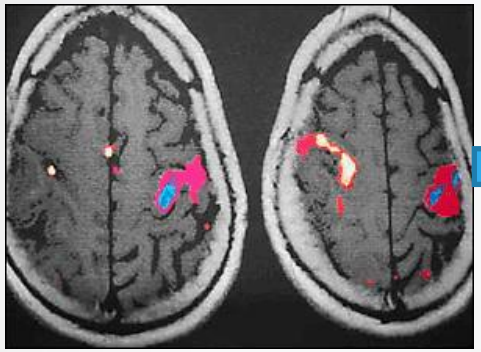
Biopsy versus resection for the management of low-grade gliomas

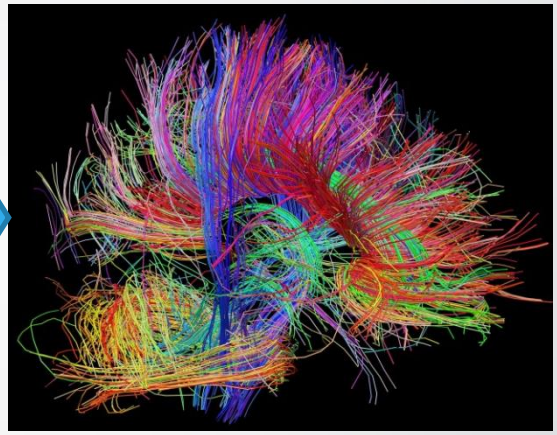
Veeravagu A, Jiang B, Ludwig C, Chang SD, Black KL, Patil CG.

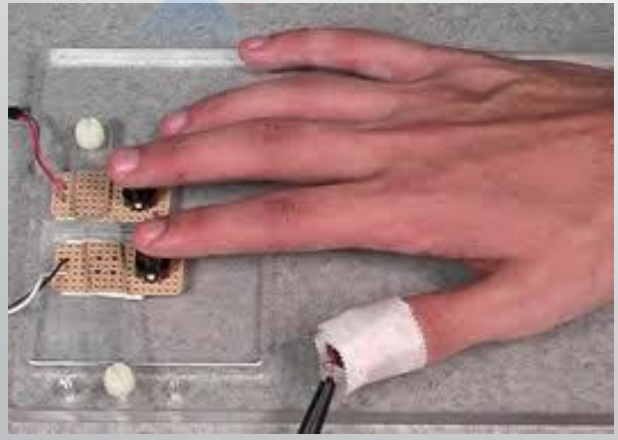
- **Selection criteria** Patients of any age with a suspected intracranial LGG receiving biopsy or resection within a randomized clinical trial (RCT) or controlled clinical trial (CCT) were included.
- **Data collection and analysis** A total of **2764 citations** were searched and critically analyzed for relevance.

- Currently there are **no randomized clinical trials or controlled clinical trials** available on which to base clinical decisions. **Therefore, physicians must approach each case individually and weigh the risks and benefits of each intervention until further evidence is available.** Future research could focus on randomized clinical trials to determine outcomes benefits for biopsy versus resection.

Functional MRI



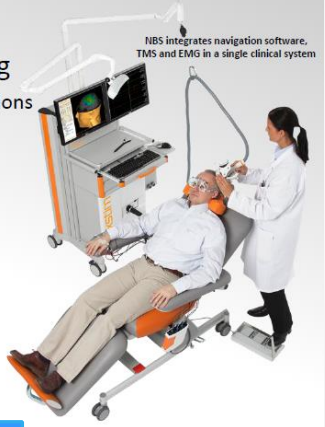


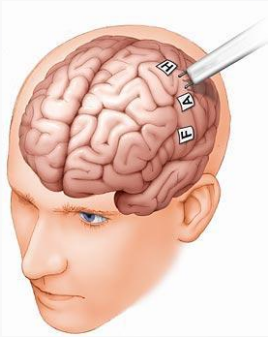


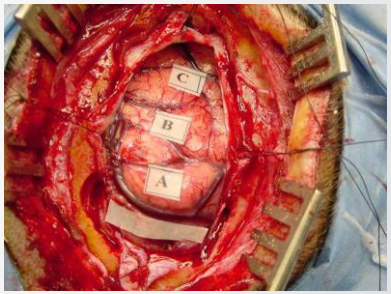
Eloquent areas
Critical Connections

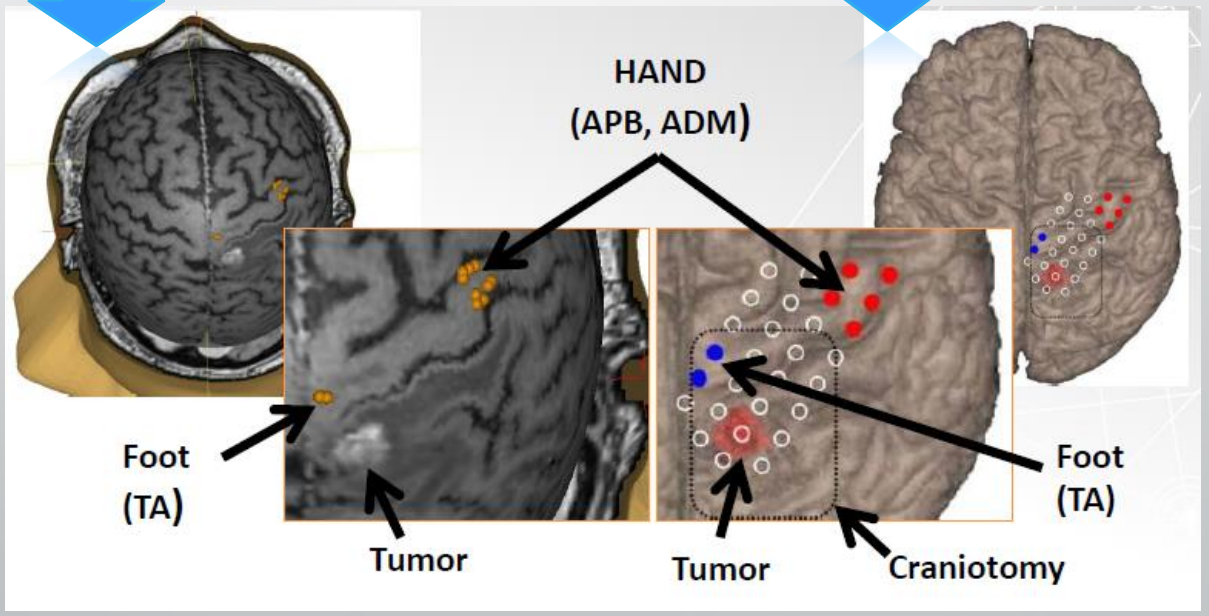
Preoperative MRI/MAG mapping vs **Per**operative/DCS mapping

- Non invasive cortical mapping
  - Neurosurgery - tumors/AV Malformations
  - Epilepsy surgery
  - Stereotactic radiosurgery
  - Motor cortex stimulation (implants)
  - Neurodiagnostics (TBI, Trauma, etc)





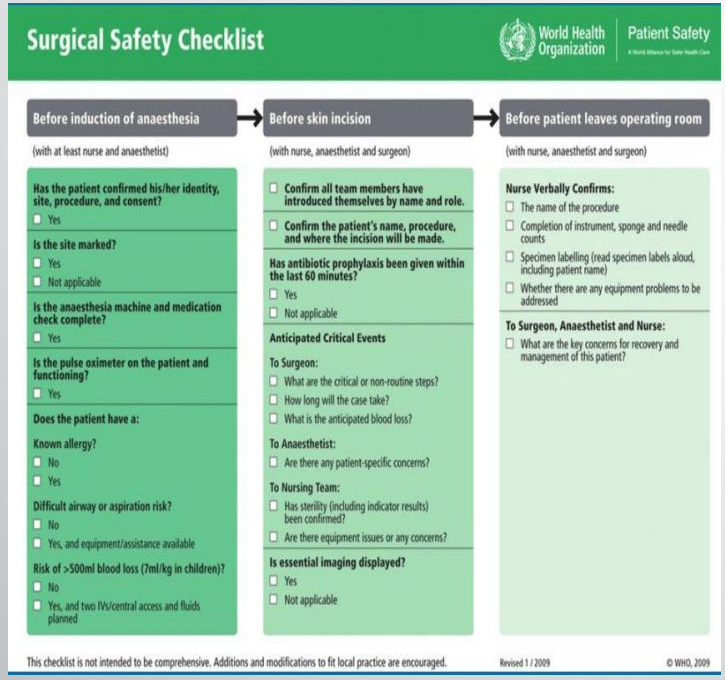




Reducing Surgical Errors

Consent

Patient Marked –~~Wrong side~~ Surgery



Surgical Safety Checklist

World Health Organization | Patient Safety

Before induction of anaesthesia (with at least nurse and anaesthetist)	Before skin incision (with nurse, anaesthetist and surgeon)	Before patient leaves operating room (with nurse, anaesthetist and surgeon)
Has the patient confirmed his/her identity, site, procedure, and consent? ☐ Yes	☐ **Confirm all team members have introduced themselves by name and role.**	**Nurse Verbally Confirms:**
Is the site marked? ☐ Yes ☐ Not applicable	☐ **Confirm the patient's name, procedure, and where the incision will be made.**	☐ The name of the procedure
Is the anaesthesia machine and medication check complete? ☐ Yes	**Has antibiotic prophylaxis been given within the last 60 minutes?** ☐ Yes ☐ Not applicable	☐ Completion of instrument, sponge and needle counts
Is the pulse oximeter on the patient and functioning? ☐ Yes	**Anticipated Critical Events**	☐ Specimen labelling (read specimen labels aloud, including patient name)
Does the patient have a:	**To Surgeon:**	☐ Whether there are any equipment problems to be addressed
Known allergy? ☐ No ☐ Yes	☐ What are the critical or non-routine steps?	**To Surgeon, Anaesthetist and Nurse:**
Difficult airway or aspiration risk? ☐ No ☐ Yes, and equipment/assistance available	☐ How long will the case take?	☐ What are the key concerns for recovery and management of this patient?
Risk of >500ml blood loss (7ml/kg in children)? ☐ No ☐ Yes, and two IVs/central access and fluids planned	☐ What is the anticipated blood loss?	
	To Anaesthetist: ☐ Are there any patient-specific concerns?	
	To Nursing Team: ☐ Has sterility (including indicator results) been confirmed? ☐ Are there equipment issues or any concerns?	
	Is essential imaging displayed? ☐ Yes ☐ Not applicable	

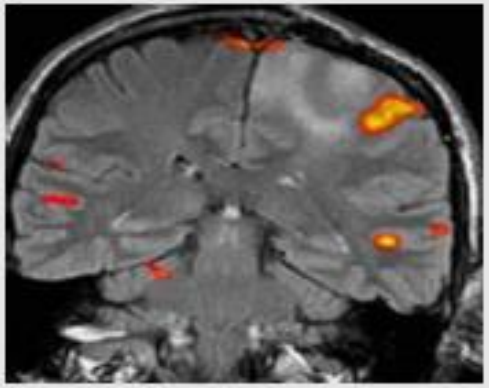
This checklist is not intended to be comprehensive. Additions and modifications to fit local practice are encouraged. Revised 1 / 2009 © WHO, 2009

WHO Checklist

UK Audit April 2015 98.7% Compliance

You must do this

Identification of functional relevant areas

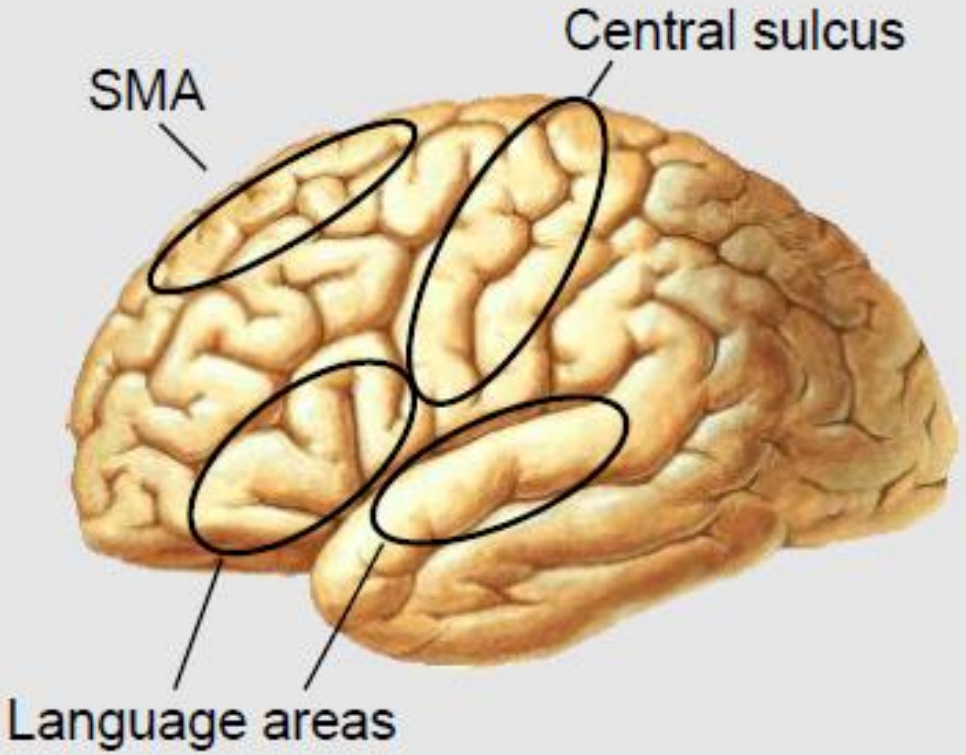


- fMR

- intraoperative mapping
  - Stimulation electrode
  - Grids
  - Phase reversal

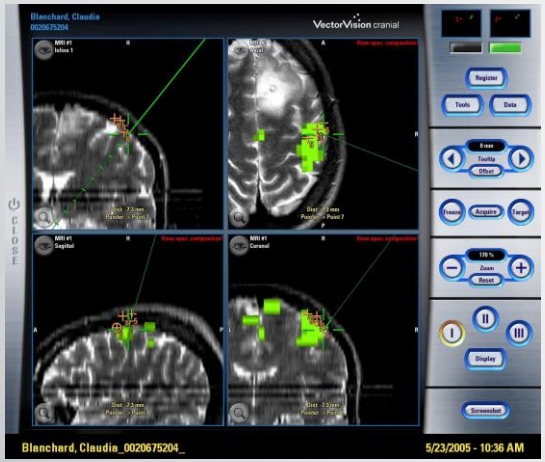
(central fissure)

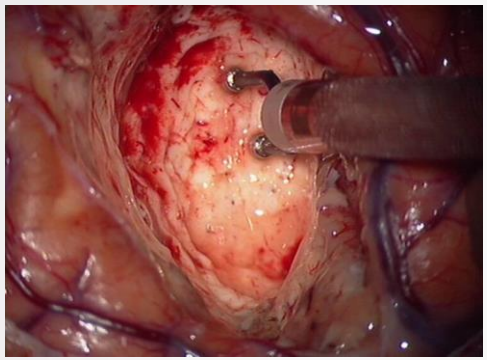
- awake craniotomy for language monitoring

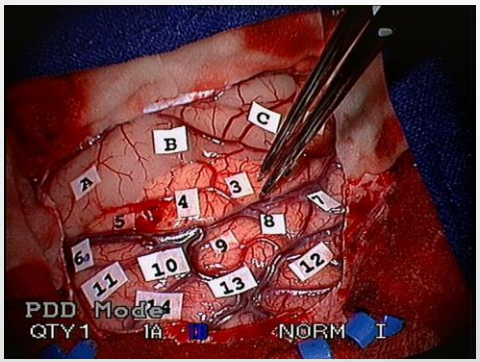


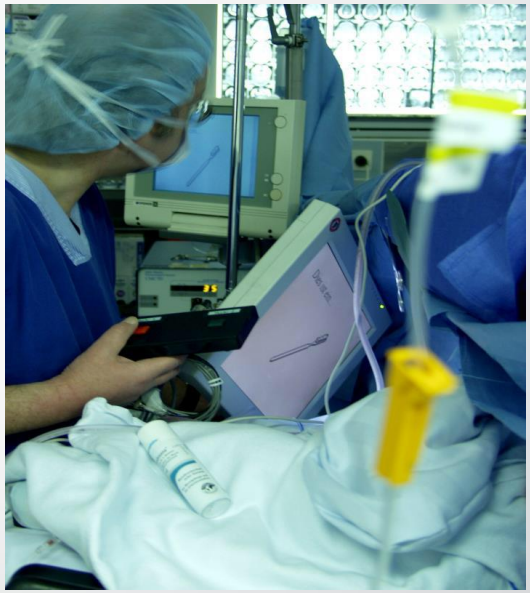
Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis.

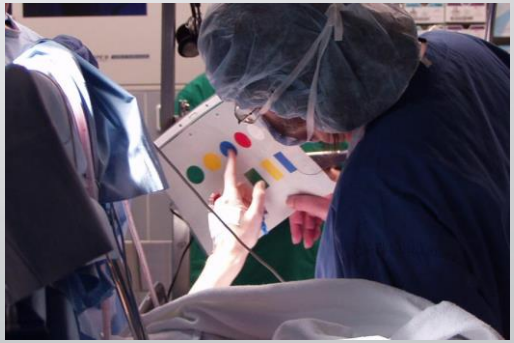
De Witt Hamer PC et al, J Clin Oncol. 2012 Jul 10;30(20):2559-65









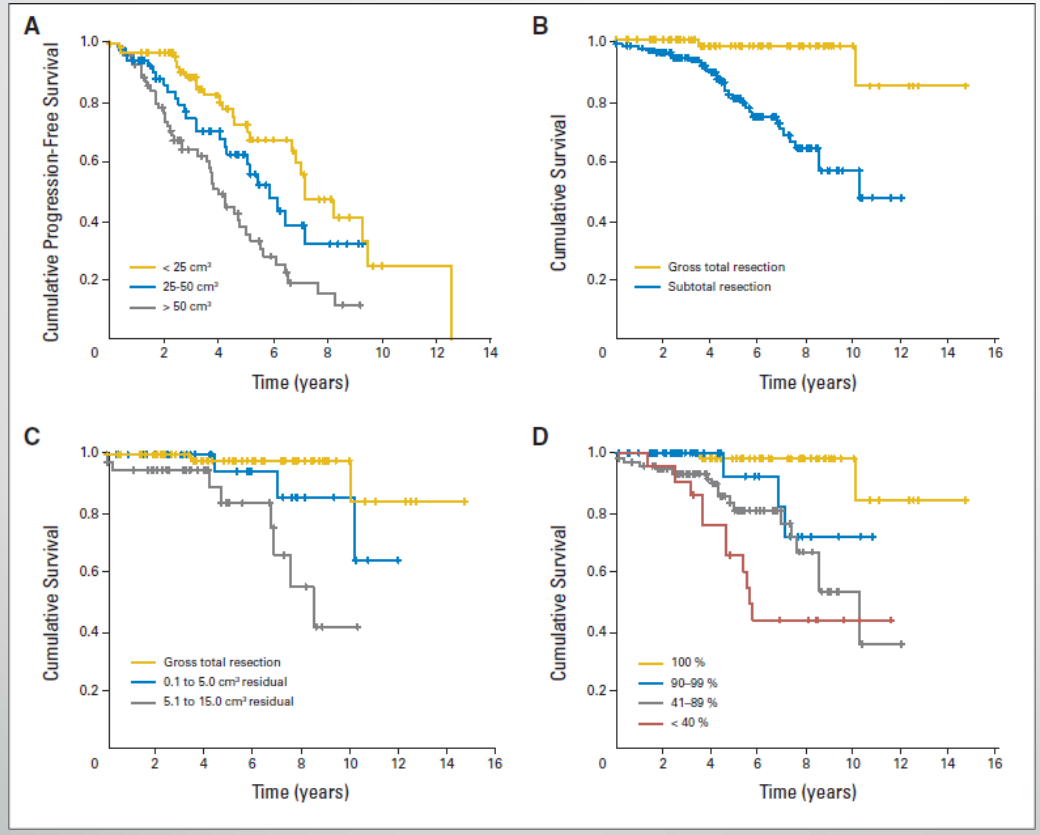


Permanent severe neurological deficit:
– 3.4% with mapping
– 8.2% without mapping

"Gross Total Resection" (as by post-OP MRI):
– 75% with mapping
– 58% without mapping

Role of Extent of Resection in the Long-Term Outcome of Low-Grade Hemispheric Gliomas

Justin S. Smith, Edward F. Chang, Kathleen R. Lamborn, Susan M. Chang, Michael D. Prados, Soonmee Cha, Tarik Tihan, Scott VandenBerg, Michael W. McDermott, and Mitchel S. Berger



Is it Safe to resect large amounts of tissue containing tumour?

VOLUME 26 · NUMBER 8 · MARCH 10 2008

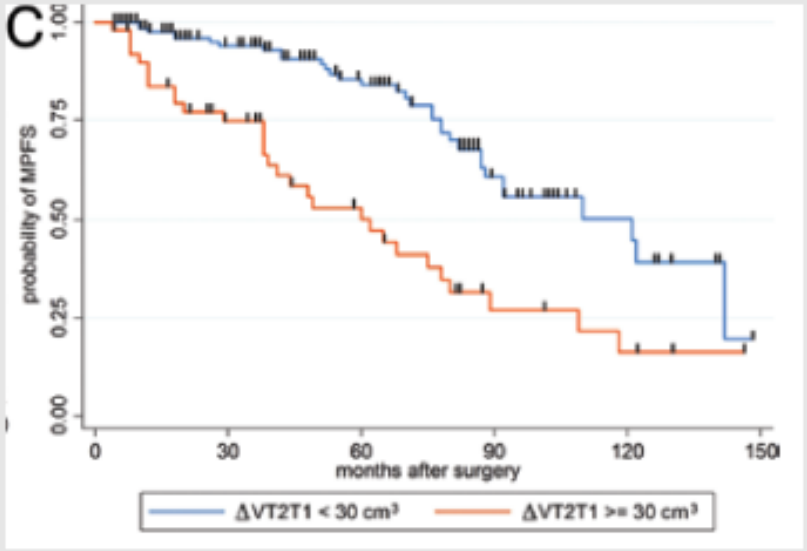
JOURNAL OF CLINICAL ONCOLOGY

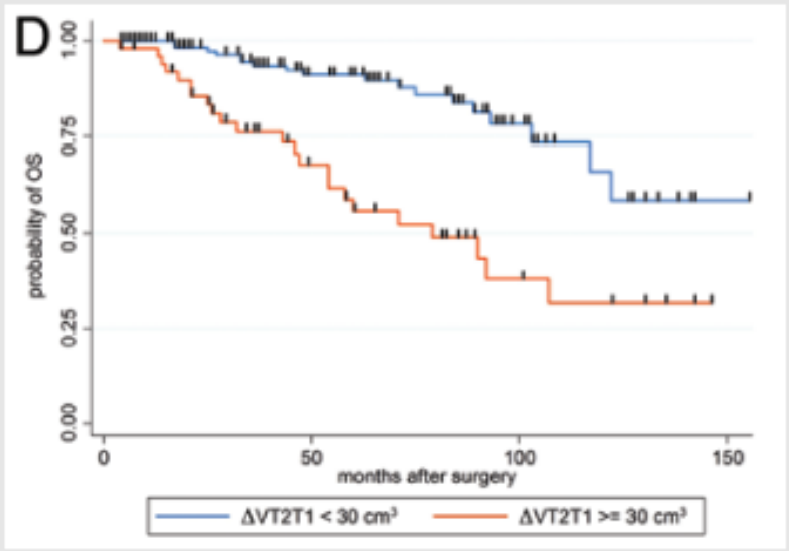
Does it Impact on the Natural History of Low Grade Glioma?

J Neurosurg 117:1039–1052, 2012

Low-grade glioma surgery in eloquent areas: volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients

Tamara Ius, M.D.,[1,2] Miriam Isola, Ph.D.,[3] Riccardo Budai, M.D.,[4] Giada Pauletto, M.D., Ph.D.,[4] Barbara Tomasino, Ph.D.,[5] Luciano Fadiga, M.D., Ph.D.,[2,6] and Miran Skrap, M.D.[1]



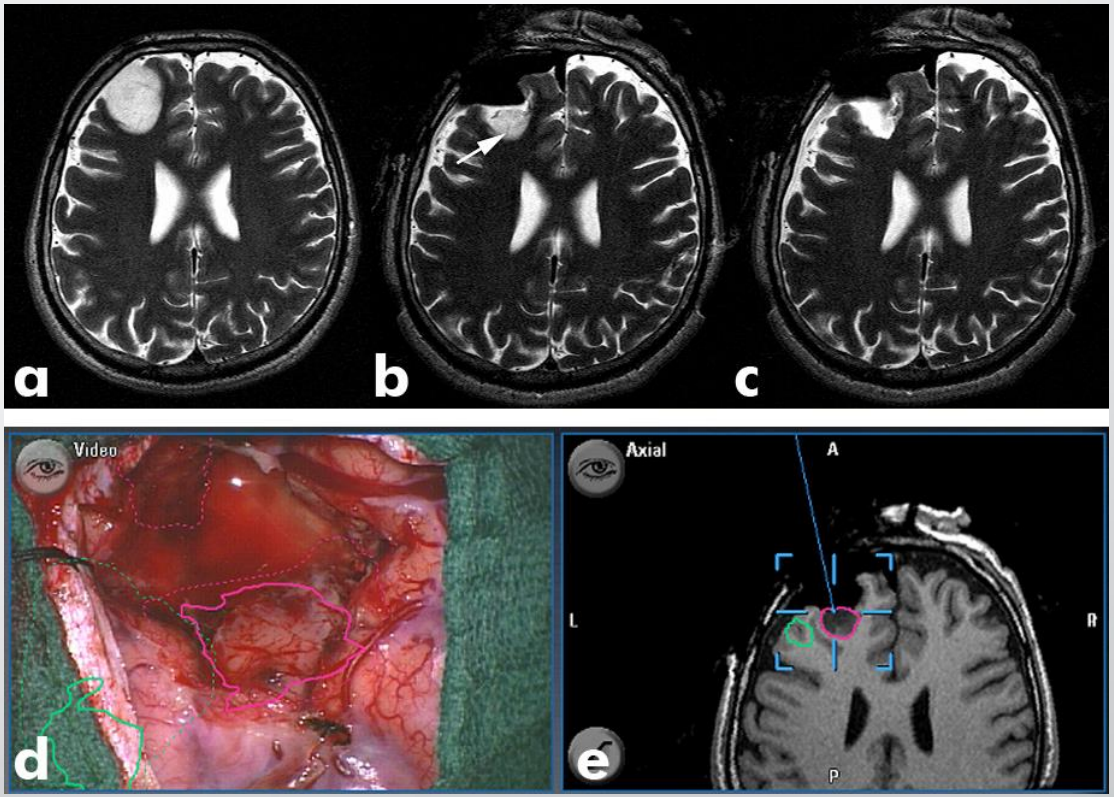


	OS			PFS			MPFS		
Factor	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
age†	1.035	1.011–1.060	0.003		NS			NS	
histological subtype‡	2.974	1.401–6.315	0.005		NS		3.202	1.489–6.886	0.003
% EOR†	0.958	0.936–0.981	0.001	0.940	0.924–0.956	<0.0001	0.963	0.944–0.982	<0.0001
ΔVT2T1†	1.035	1.017–1.054	<0.0001	1.021	1.008–1.034	0.001	1.029	1.014–1.045	<0.0001

Intraoperative MRI

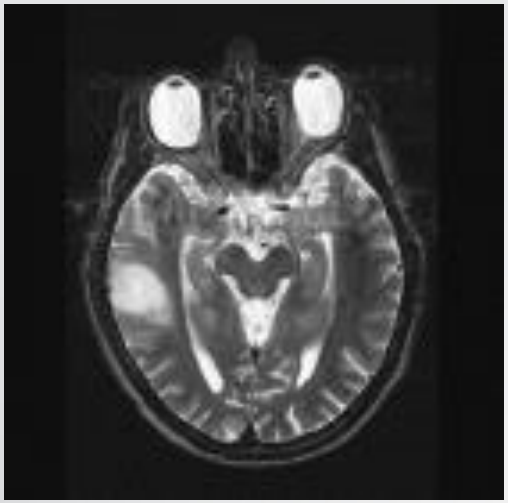
BrainSUITE iMRI Clinical Images

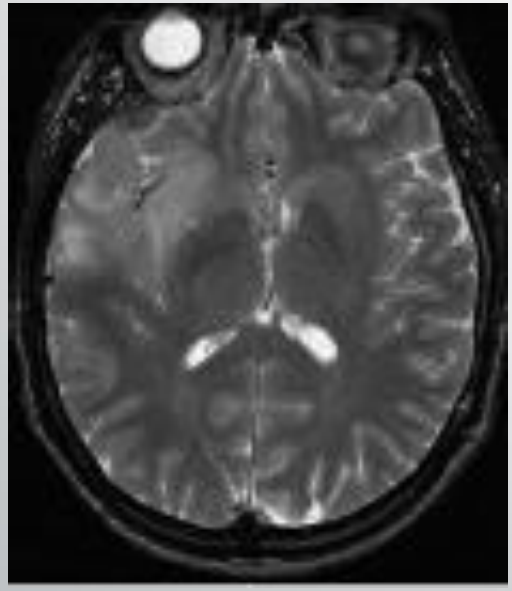
Left frontal WHO grade II Astrocytoma
a-c: Stages of tumor resection through intra-operative T2-weighted imaging
d: Microscope view with overlayed, updated intra-operative imaging
e: Navigation screen with automatically registered intra-operative T-1weighted images

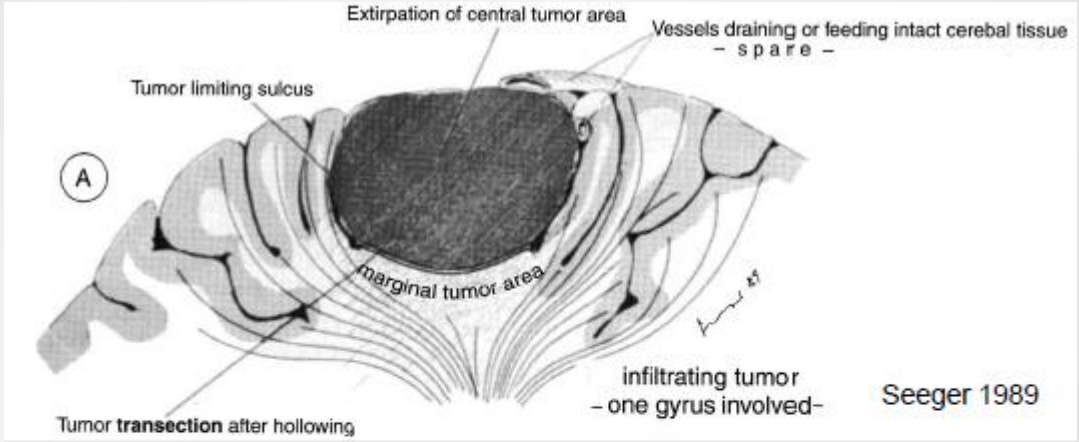


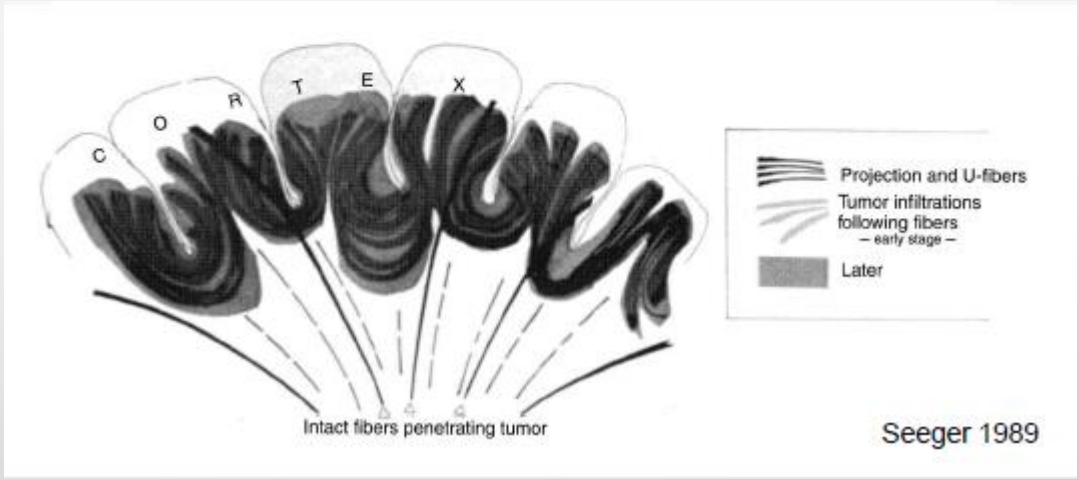
Expensive ? Cumbersome? Precise?

Images are courtesy of C. Nimsky, Erlangen-Nuremberg University, Germany

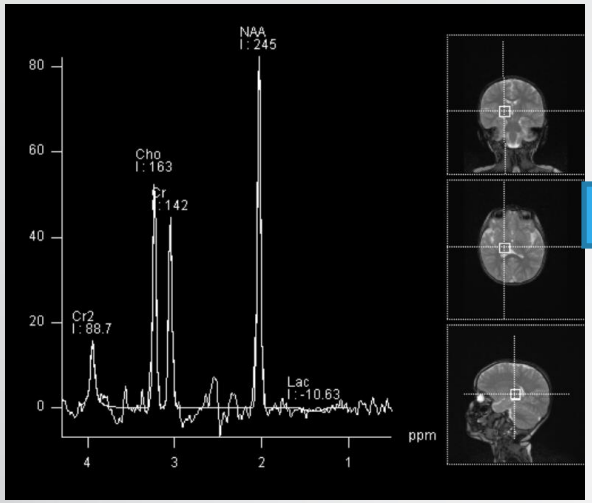


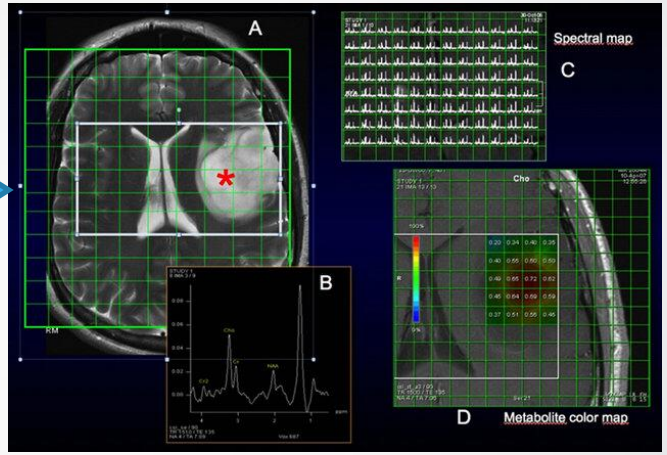



Extirpation of central tumor area
Vessels draining or feeding intact cerebal tissue
– s p a r e –
Tumor limiting sulcus
A
marginal tumor area
infiltrating tumor
– one gyrus involved–
Tumor transection after hollowing
Seeger 1989

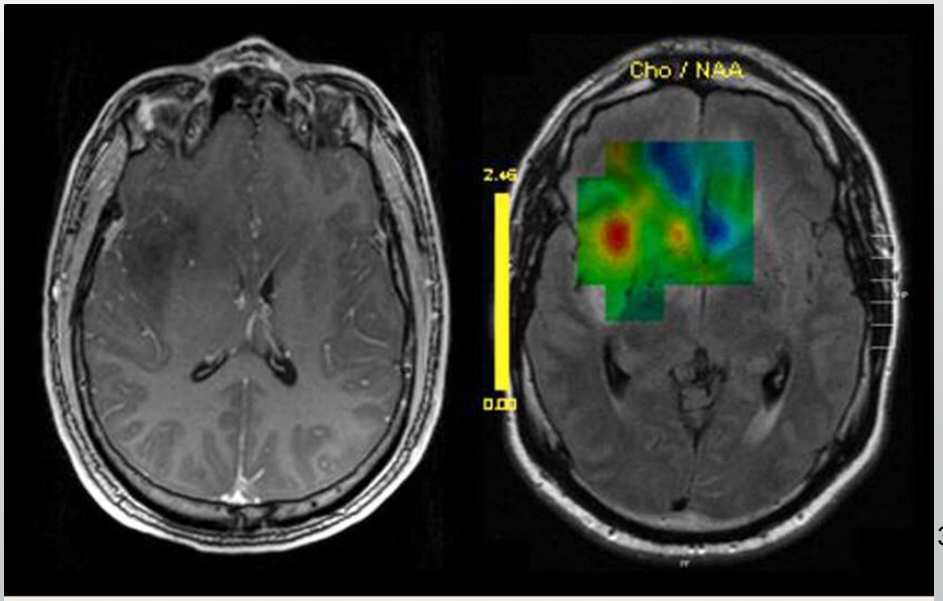

C
O
R
T
E
X
Projection and U-fibers
Tumor infiltrations following fibers
– early stage –
Later
Intact fibers penetrating tumor
Seeger 1989

Choline Mapping





Clever Imaging
to find 'bad' areas
can help define
surgical
approach/target

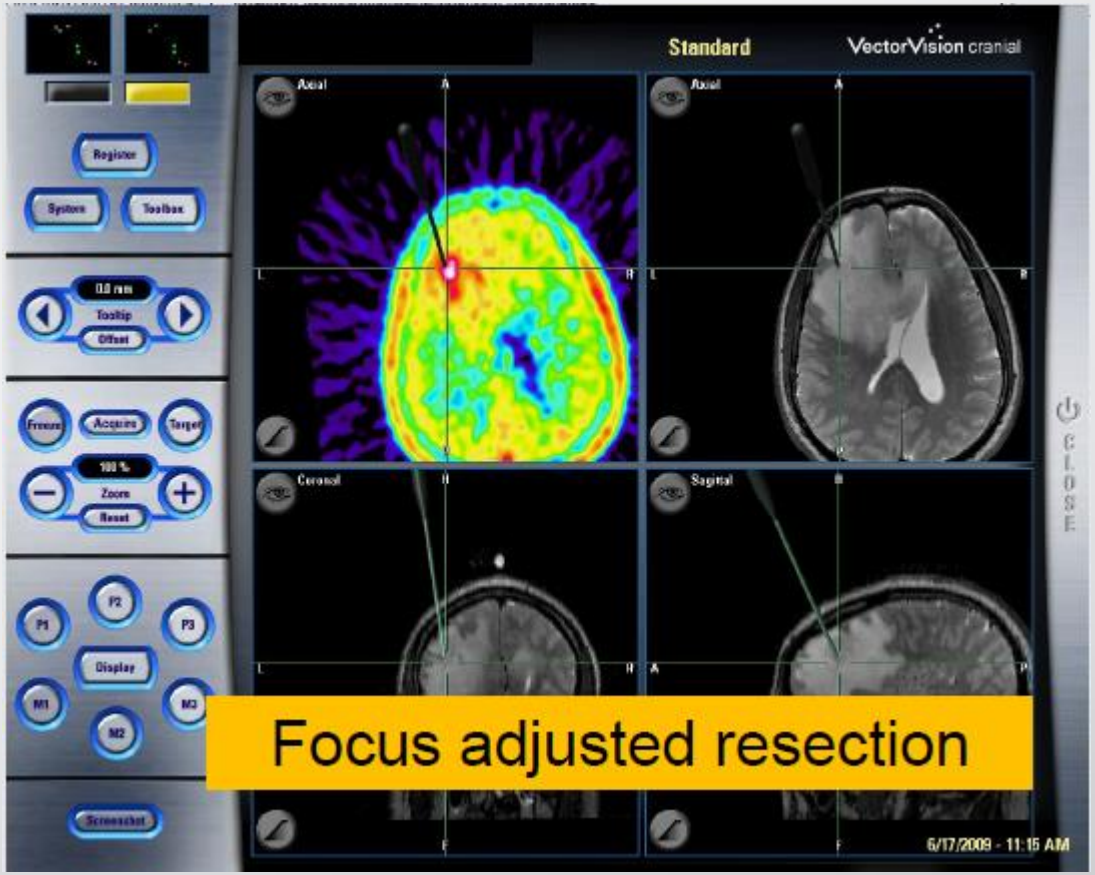


Optimal? Approach to Diffuse Low Grade Gliomas

MRI:
Flair pattern

MRS:
Choline Mapping

PET:
Methionine
FDG

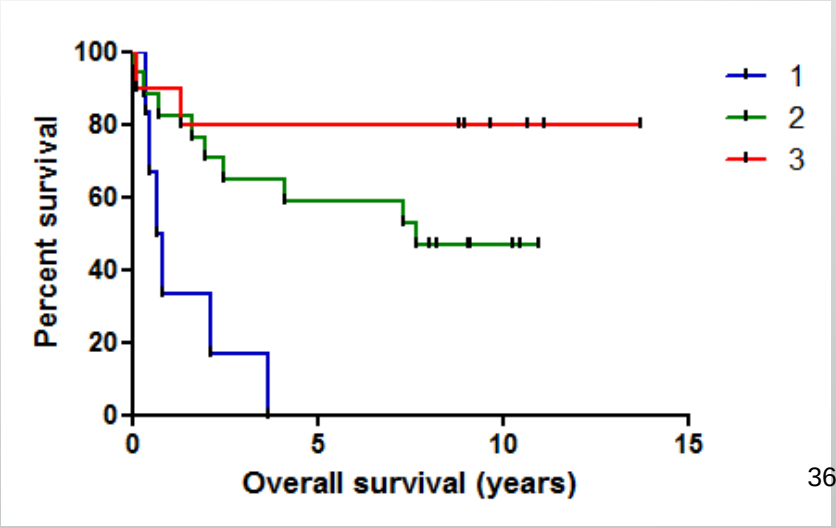


Diffuse Tumours

Individualised Therapy

- Genetic profile of LGG essential for management and access to trials
- Recent genomic studies on 'defined' LGG show a small number contain genes highly predictive of rapid transformation
- This Means that **All Low Grades** must be adequately biopsied at presentation
- Game Changer !

Using our gene expression analysis approach, we may be able to prospectively identify patients for whom radical treatment approaches are indicated



Tennant D, Cruickshank G et al 2015

Surgical Strategy – „low grade“ glioma

- Patients with **radiologically circumscribed, „resectable“ glioma**
  → microsurgical resection
- Patients with **nonresectable, diffuse** glioma / diffuse glioma in eloquent area → biopsy including molecular signature
- Try to **identify**, characterize (and remove) **anaplastic foci**
- **Avoid additional surgical morbidity ! Imaging & Neuromonitoring**

Many Patients with Low Grade Tumours require anticonvulsant drugs and may suffer disabling dose and side effects
– these should be considered for early/further resection
as >80% will obtain dose improvement and better seizure control

All GBM patients do better with Aggressive Therapy?

10,743 pts

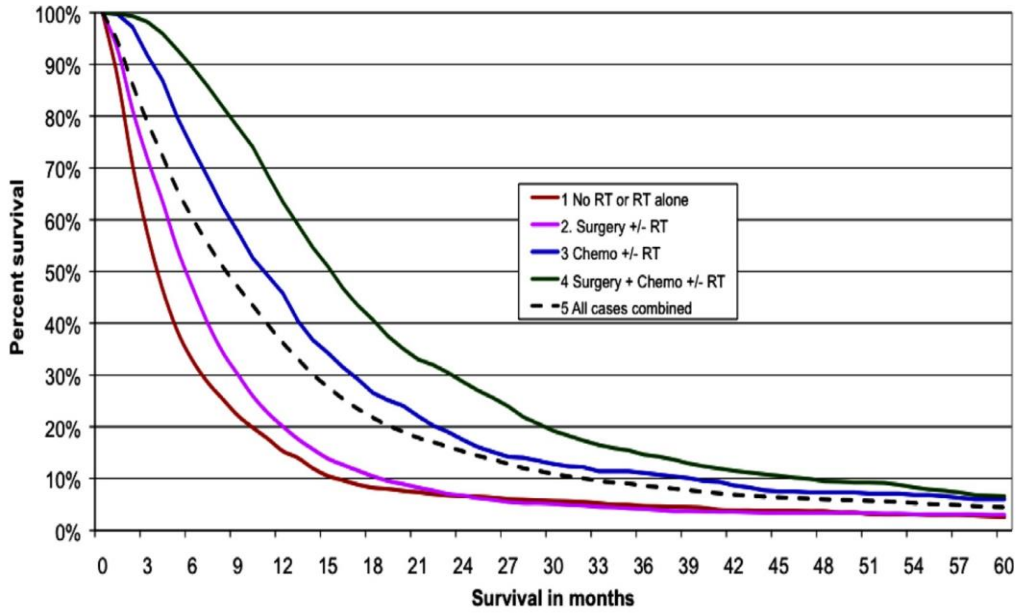


Fig. 6. Kaplan–Meier plot demonstrating survival by treatment type for patients with glioblastoma 20–70 years of age (2007–2010). RT: Radiotherapy. Radiotherapy data is not complete, but it is likely that most of the patients in groups 2–4 under 70 years of age received radiotherapy. Chemo: Chemotherapy. Surgery is any debulking procedure and does not include biopsy. There were significant differences between all treatment groups ($p < 0{\cdot}0001$).

Brodbelt A, Greenberg D et al National Cancer Information network Glioblastoma in England 2007- 2011 Eur J Cancer April 2015

Older patients – as well?

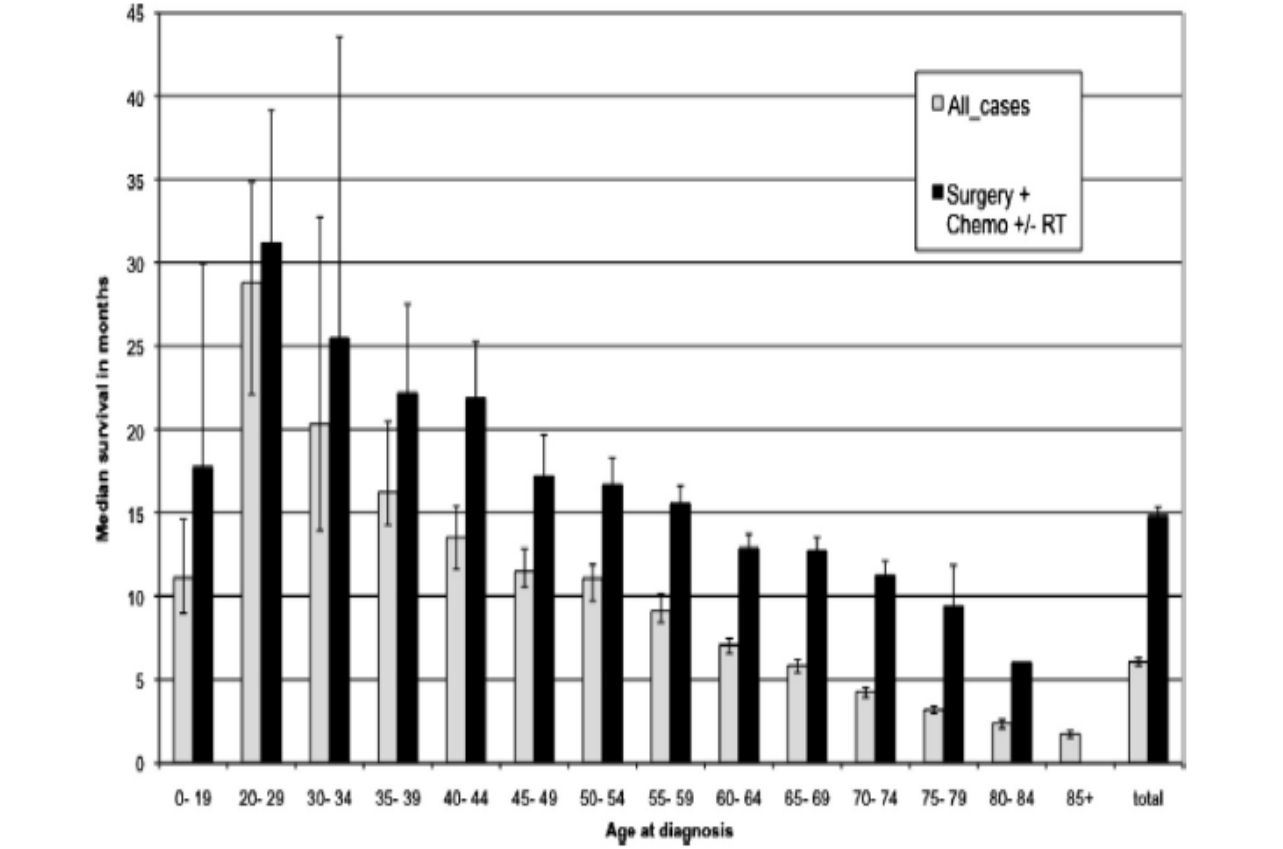


Fig. 8. Median survival of all patients by age compared to those treated with surgery, chemotherapy (Chemo), +/– radiotherapy (RT): 2007–2010. Radiotherapy data is not complete, but it is likely that most of the patients in this group under 70 years of age received radiotherapy.

A HUGE Challenge for the future !

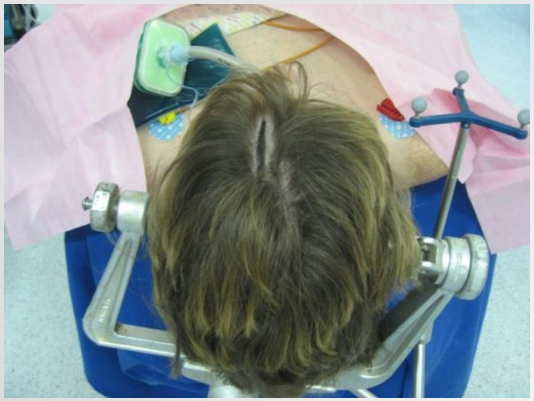
High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

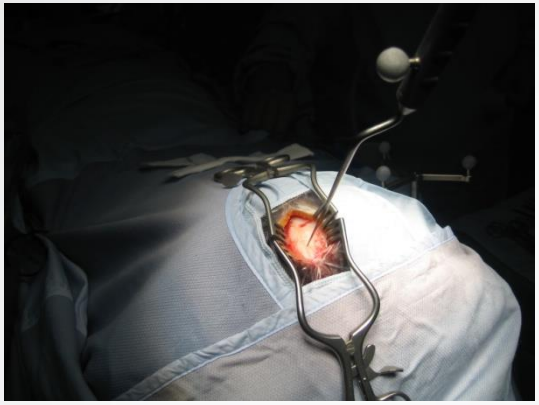
R. Stupp[1], J.-C. Tonn[2], M. Brada[3] & G. Pentheroudakis[4]
On behalf of the ESMO Guidelines Working Group*

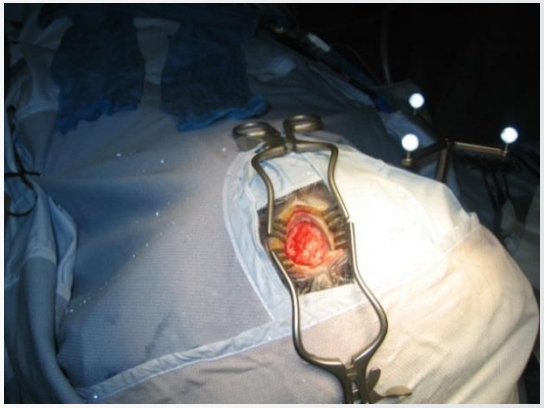
Tumour resection is of prognostic value; it may be beneficial to attempt maximal tumour resection provided that neurological function is not compromised by the extent of resection [II, C]. When microsurgical resection is not safely feasible (e.g. due to location of the tumour or impaired clinical condition of the patient), a stereotactic serial biopsy should be performed. The diagnostic yield is >95% in experienced hands, moreover molecular genetic analyses (LOH 1p/19q, *MGMT* promoter methylation) can be performed on freshly frozen

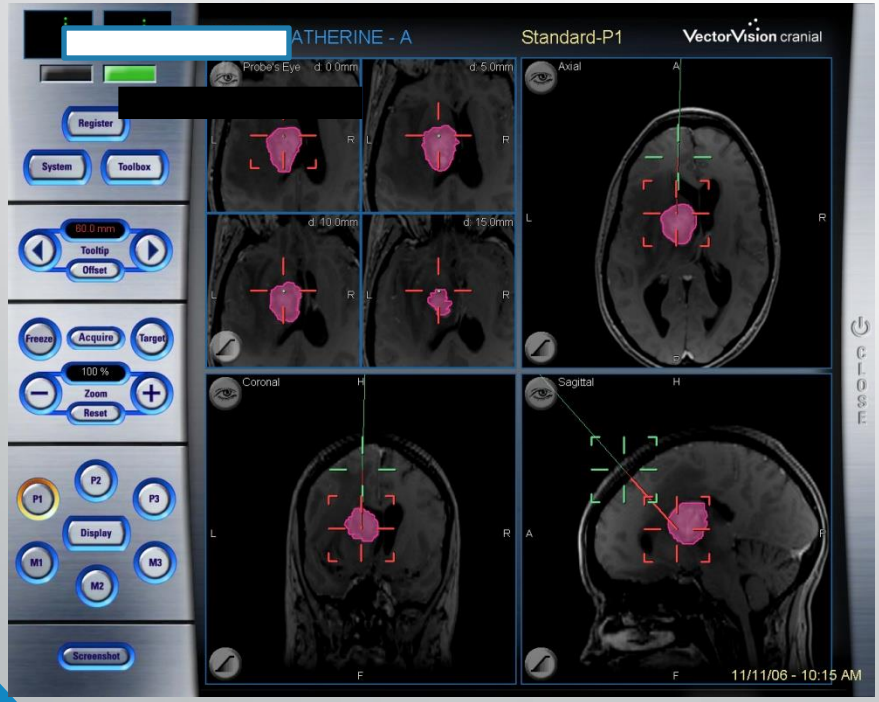
Annals of Oncology 21 (Supplement 5): v190–v193, 2010

Image Directed Surgery







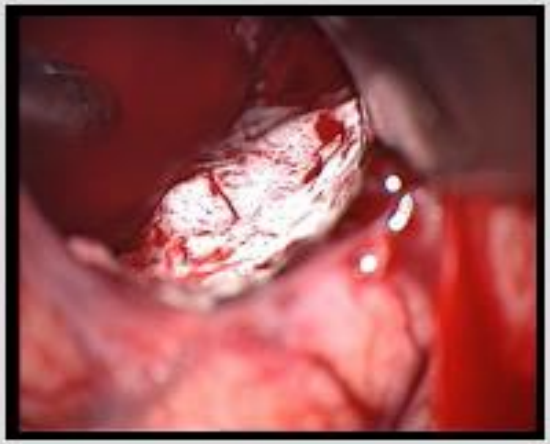


Minimal Disturbance
Precise access to tumours
Awake- Negative Mapping
5 ALA Microscope Resection
Rapid access, and closure

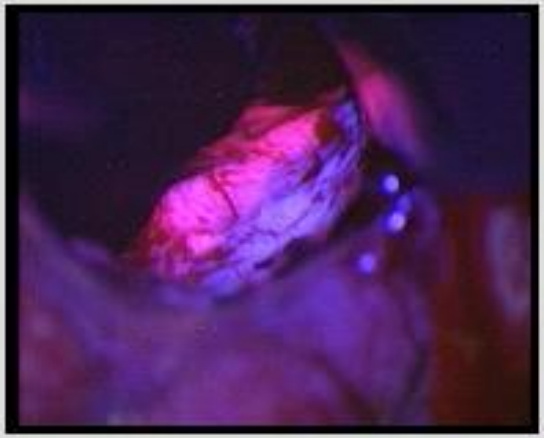
Day Case Craniotomy??

Microsurgery

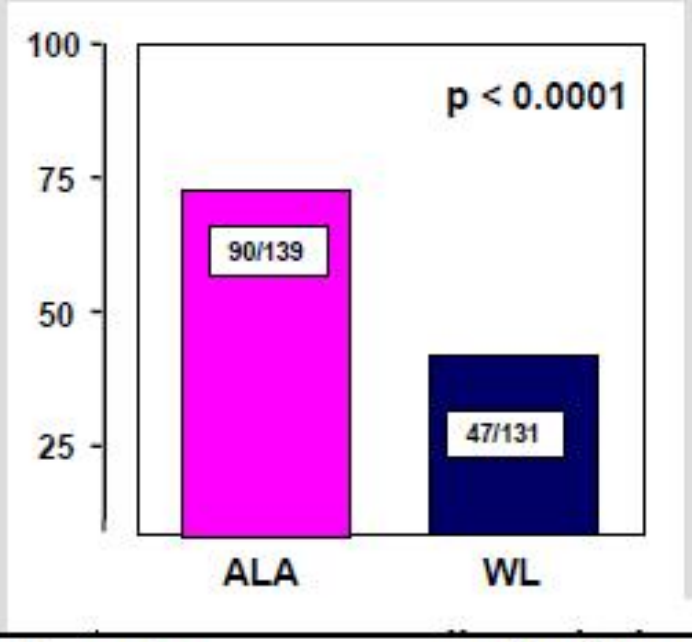
- Improved results due to fluorescence guided resection
  (Stummer et al., Lancet Oncol 2006)



white light

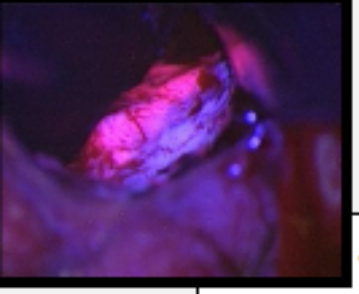


ALA
UV-light



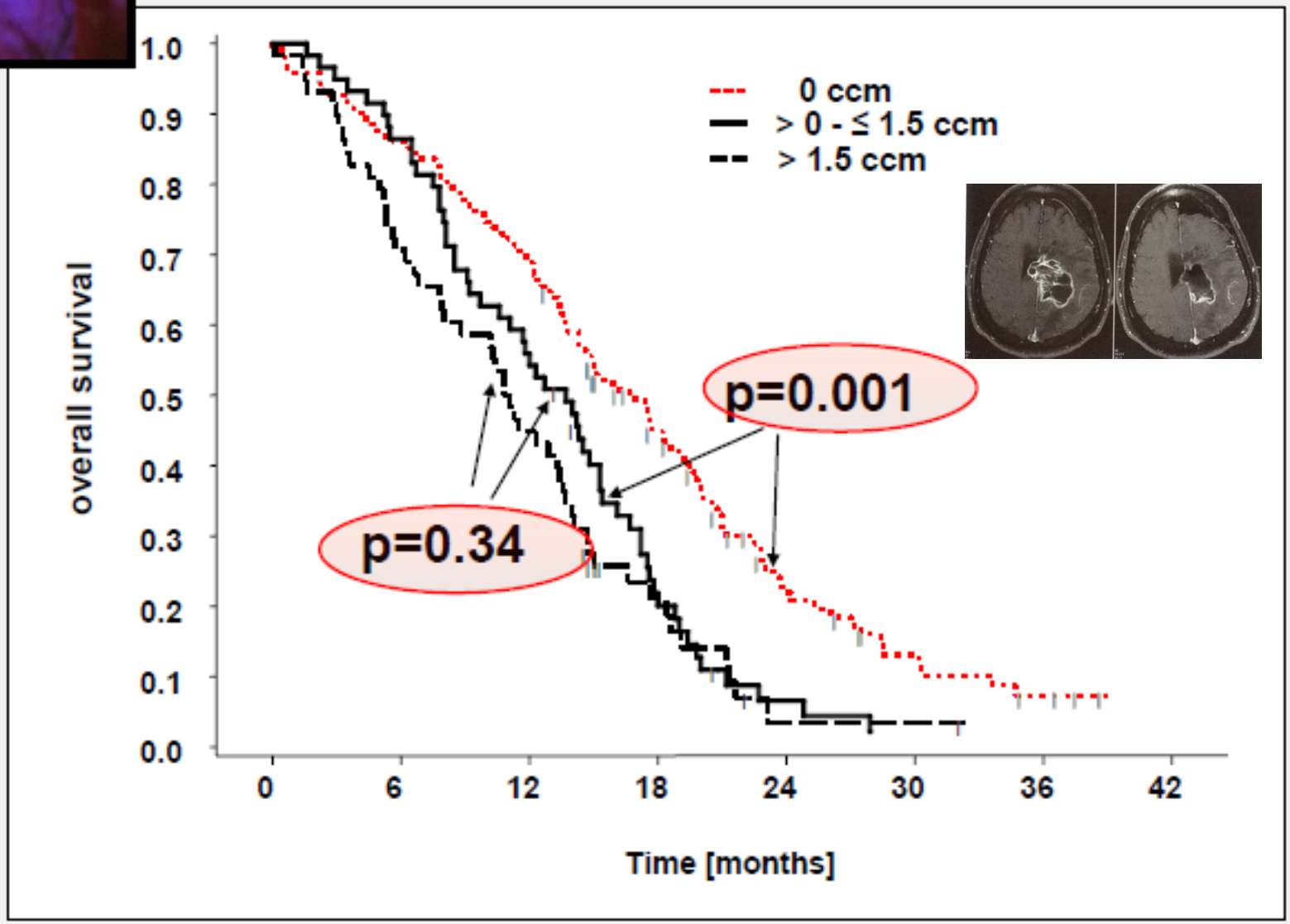
Parameter	multivariate *p* value
* *Residual tumor no / yes*	0.0006
* *KPS ≤ 80 / >80*	0.0055
Age ≤ 55 / > 55	0.0132
Eloquent areas no / yes	0.2144

* Gadolinium Enhanced Post Operative MRI



Fluorescence Guided Resection (5-ALA):

Overall survival stratified by residual tumor volume



(Stummer et al., Lancet Oncol 2006)

What is the Impact of this Policy?

Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy†

F. -W. Kreth[1,‡], N. Thon[1,‡], M. Simon[2], M. Westphal[3], G. Schackert[4], G. Nikkhah[5], B. Hentschel[6], G. Reifenberger[7], T. Pietsch[8], M. Weller[9] & J. -C. Tonn[1*], for the German Glioma Network

Ann Oncol. 2013 Dec;24(12):3117-23

Surgery, *n* (%)	
Gross total resection	125 (36.2)
Incomplete resection	148 (42.9)
Biopsy	72 (20.9)

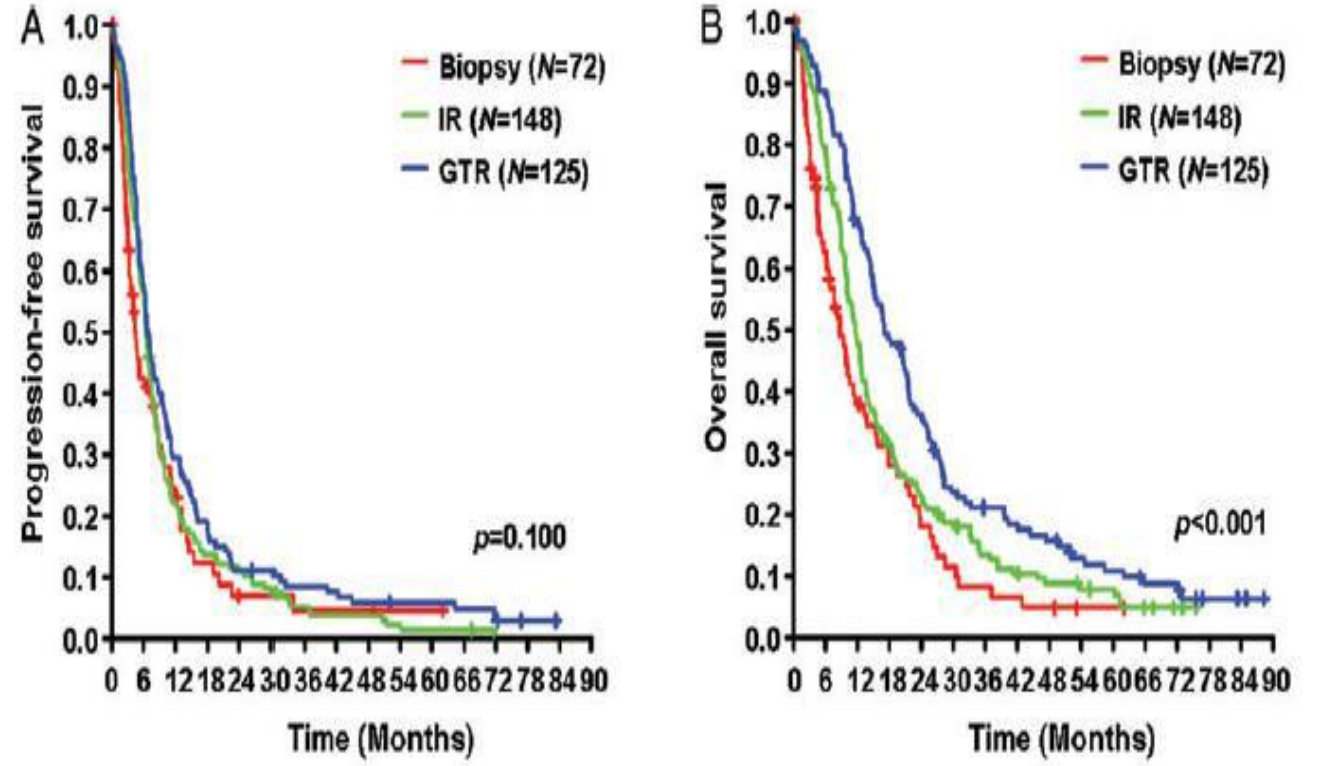
Verbundprojekt der Deutschen Krebshilfe "Glioma"

	Microsurgery (n=296)	Biopsy (n=73)	*p-value*
Dominant hemisphere location	135 (46.4%)	45 (64.3 %)	0.007
Surgery-related morbidity (overall) hemiparesis/speech disturbance intracerebral haematoma seizures others	35 (11.8%) 9 (3.0%) 9 (3.0%) 6 (2.0%) 11 (4.1%)	1 (1.4%) 1 (1.4%)	0.006
First line treatment RT plus TMZ RT alone CT alone palliative care	203 (68.8%) 60 (20.3%) 5 (1.7%) 28 (9.5%)	37 (50.7%%) 11 (15.1%) 10 (13.7%) 15 (20.5%)	<0.001
Time between diagnosis and RT plus TMZ treatment in days	25	18	<0.001

-Patient Selection
-Some will be worse off

Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy†

F. -W. Kreth[1,‡], N. Thon[1,‡], M. Simon[2], M. Westphal[3], G. Schackert[4], G. Nikkhah[5], B. Hentschel[6], G. Reifenberger[7], T. Pietsch[8], M. Weller[9] & J. -C. Tonn[1*], for the German Glioma Network



Ann Oncol. 2013 Dec;24(12):3117-23

Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study

J Neurosurg / April 16, 2010

Clinical article

Walter Stummer, M.D.,[1] Jörg-Christian Tonn, M.D.,[2] Hubertus Maximilian Mehdorn, M.D.,[3] Ulf Nestler, M.D.,[4] Kea Franz, M.D.,[6] Claudia Goetz, M.D.,[2] Andrea Bink, M.D.,[5] and Uwe Pichlmeier, Ph.D.,[7] on behalf of the ALA-Glioma Study Group*

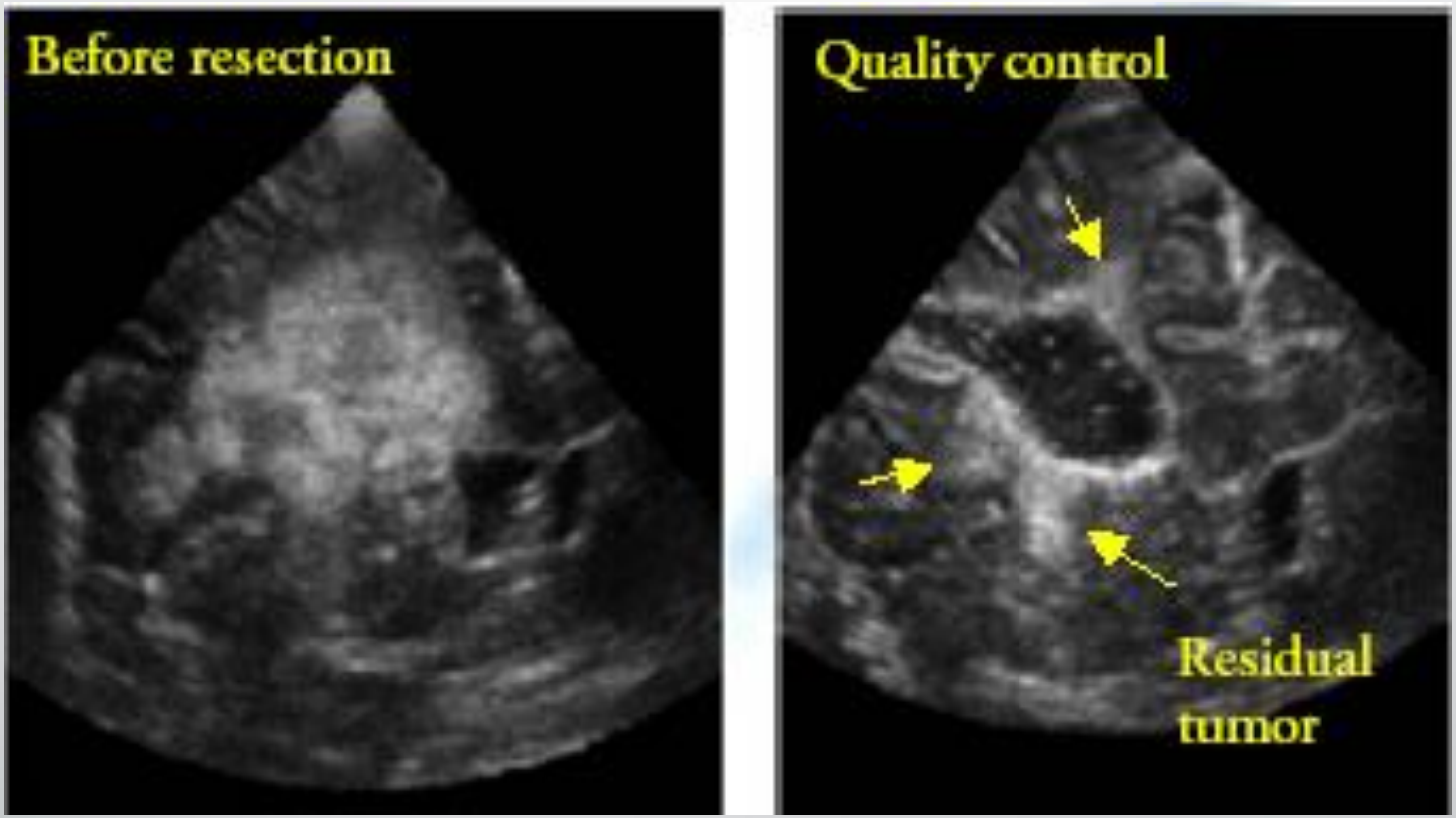
TABLE 3: Deterioration of the NIH-SS score ≥1 point compared to preoperative (baseline) score

Time	ALA Group (%)	WL Group (%)	p Value
48 hrs postop	26.2	14.5	0.02
7 days postop	20.5	10.7	0.09
6 wks postop	17.1	11.3	0.29
3 mos postop	19.6	18.6	0.77

Patients at particular risk during improved cytoreduction appeared to be those whose symptoms fail to improve with steroid premedication. Such patients appear less suitable for operations in which tools for extending resection are used.

Perhaps a useful criteria for optimising surgical resources and reducing risks to patients?

Intraoperative Ultrasound and Glioma Surgery?

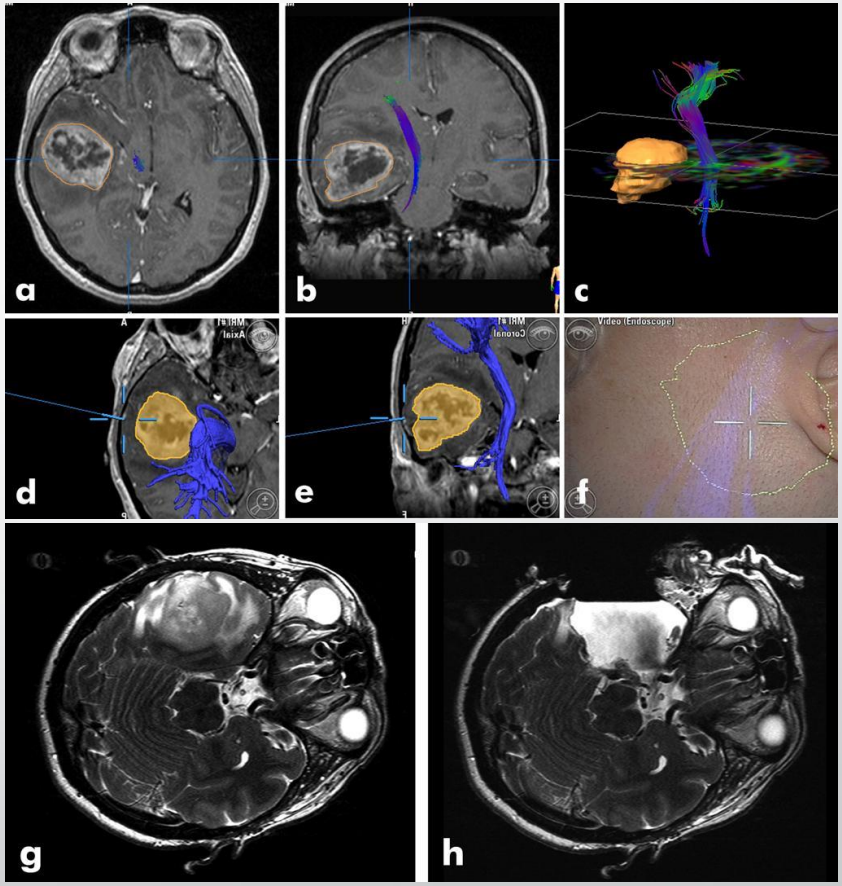


Truly intra-operative
Good for access and resection
BUT operator dependent and usefullness impaired by peroperative hyper-echoic blanking

Does Intraoperative MRI really help us ?

BrainSUITE iMRI Clinical Images

Right temporal Glioblastoma
a-c: Pre-operative planning through iPlan Surgical Planning Software including segmentation of tumor and pyramidal tract
d-f: Navigation and microscope images during the beginning of the procedure
g-h: Identical slices of pre- and intra-operative T2-weighted images visualizing extent of tumor resection



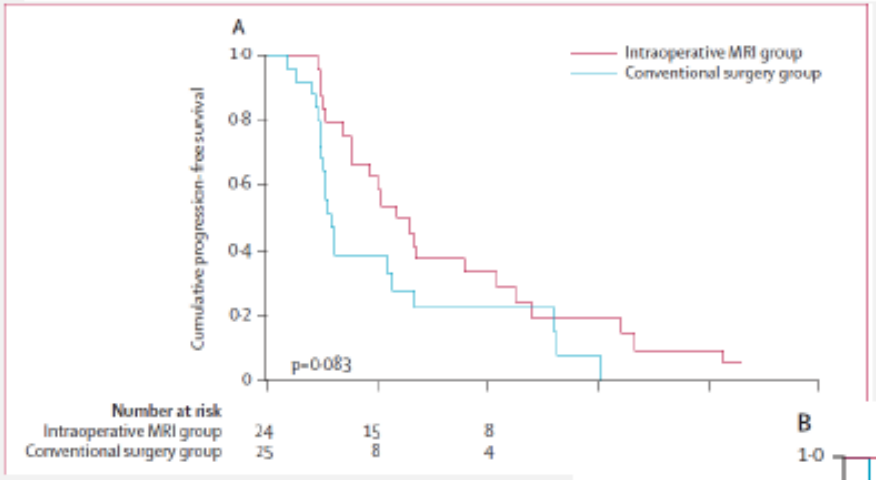
Images are courtesy of C. Nimsky, Erlangen-Nuremberg University, Germany

Paediatric Neurosurgery—Medulloblastoma surgery - ? Must Have

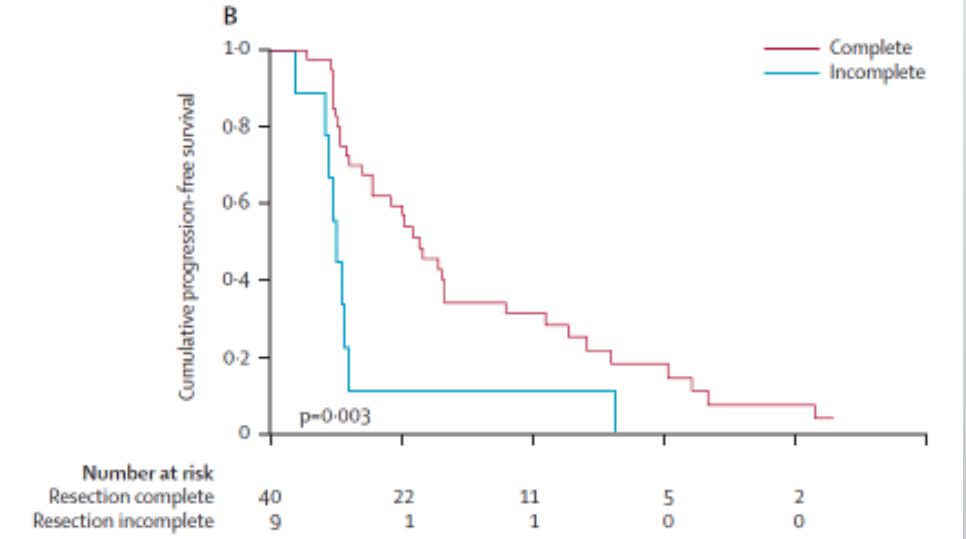
Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial

Christian Senft, Andrea Bink, Kea Franz, Hartmut Vatter, Thomas Gasser, Volker Seifert

Lancet Oncol 2011; 12: 997–1003



- MRI does not matter per se
- *Complete* resection matters
- MRI helps to achieve it



Cochrane Database Syst Rev. 2014 Jan 28;1:CD009685

Image guided surgery for the resection of brain tumours

Barone DG, Lawrie TA, Hart MG

- **METHODS:** Four RCTs were identified:
  1. iMRI (58 patients)
  2. (5-ALA) fluorescence guided surgery (322 patients)
  3. neuronavigation (45 patients)
  4. DTI-neuronavigation (238 patients)

- **FINDINGS:** There was no clear evidence of improvement in overall survival (OS) with 5-ALA or DTI-neuronavigation in patients with high grade glioma. Progression-free survival (PFS) data were not available in the appropriate format for analysis.

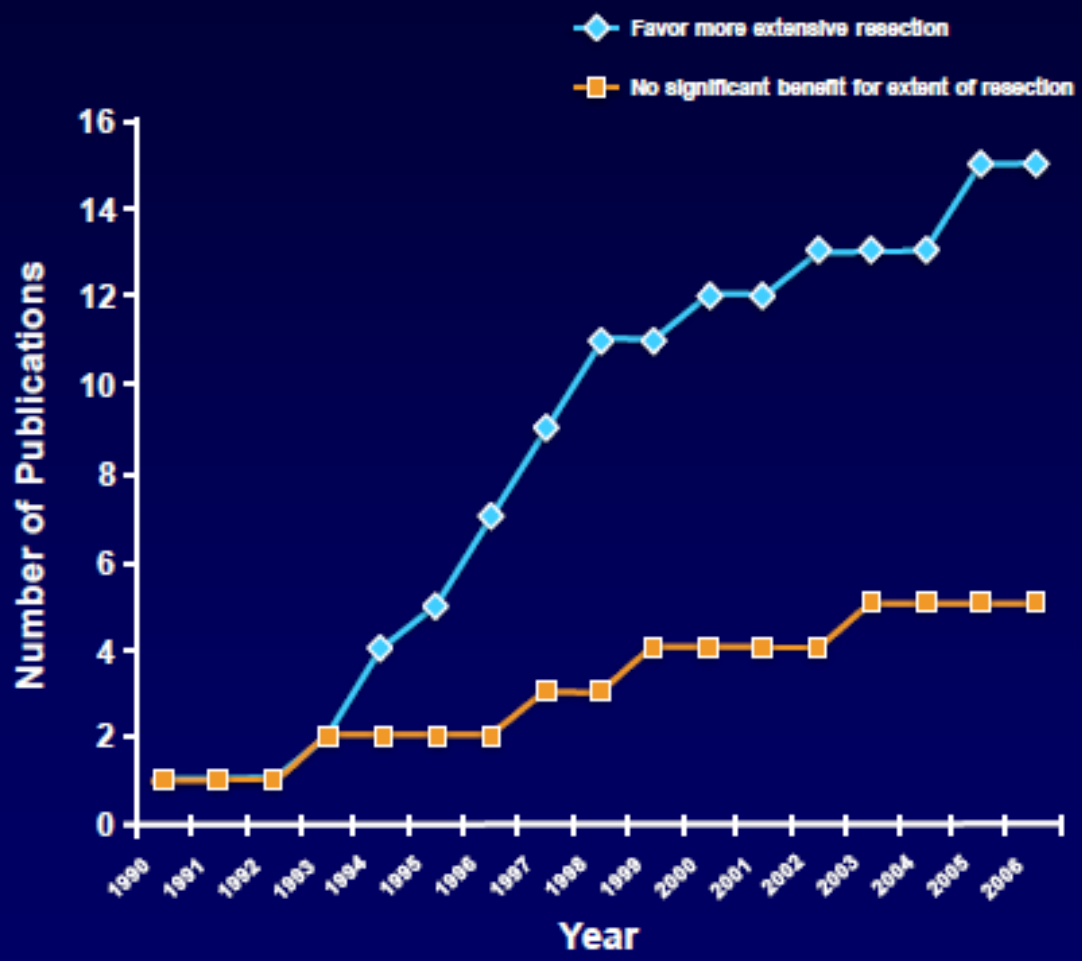
- **REVIEWER'S CONCLUSIONS:** **Effects of image guided surgery on survival and QoL are unclear.**

Glioma Extent of Resection and Its Impact on Patient Outcome

Objective: There is still no general consensus in the literature regarding the role of extent of glioma resection in improving patient outcome. Although the importance of resection in obtaining tissue diagnosis and alleviating symptoms is clear, a lack of Class I evidence prevents similar certainty in assessing the influence of extent of resection.

Methods: We reviewed every major clinical publication since 1990 on the role of extent of resection in glioma outcome.

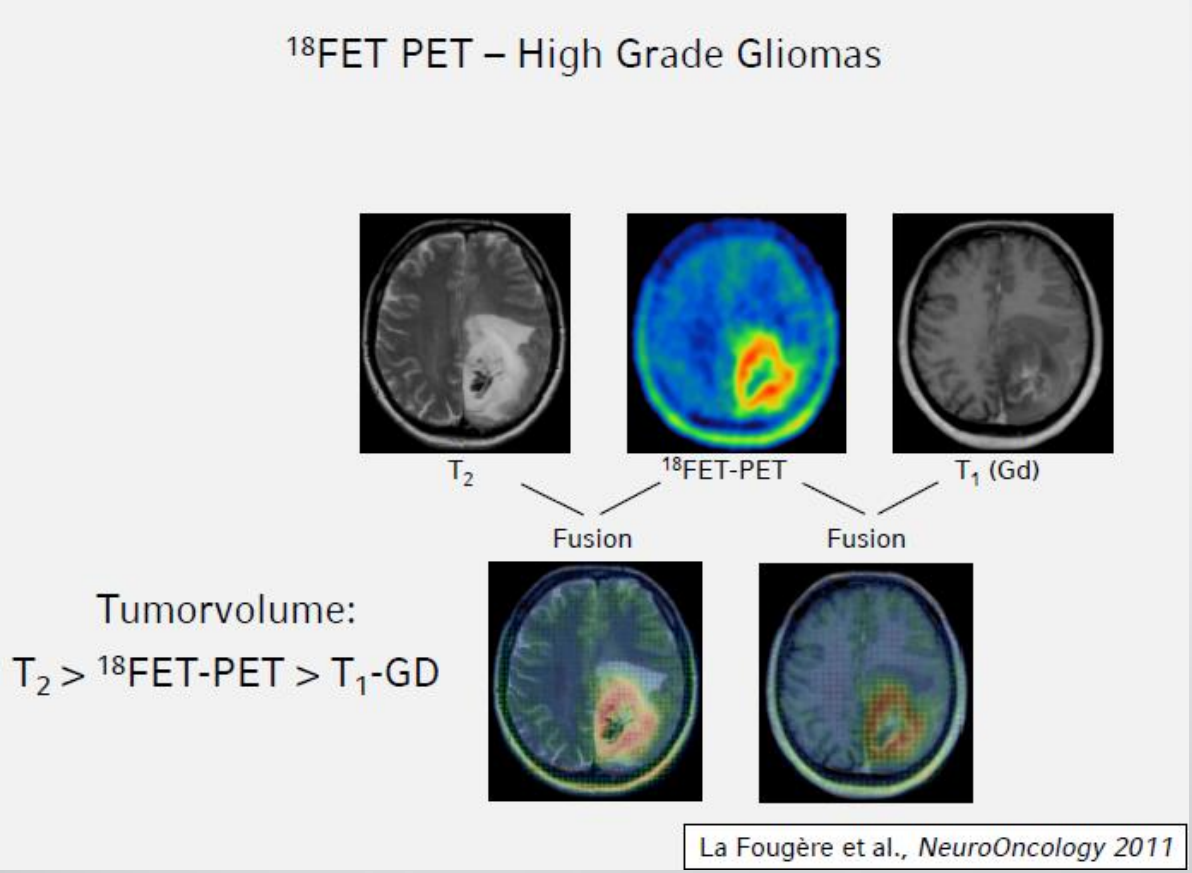
Conclusion: Despite persistent limitations in the quality of data, mounting evidence suggests that more extensive surgical resection is associated with longer life expectancy for both low- and high-grade gliomas.



Trends in the relative numbers of studies in the neurosurgical literature since 1990 statistically examining the impact of extent of resection on patient survival.

Sanai N, et al. *Neurosurgery.* 2008;62(4):753-764.

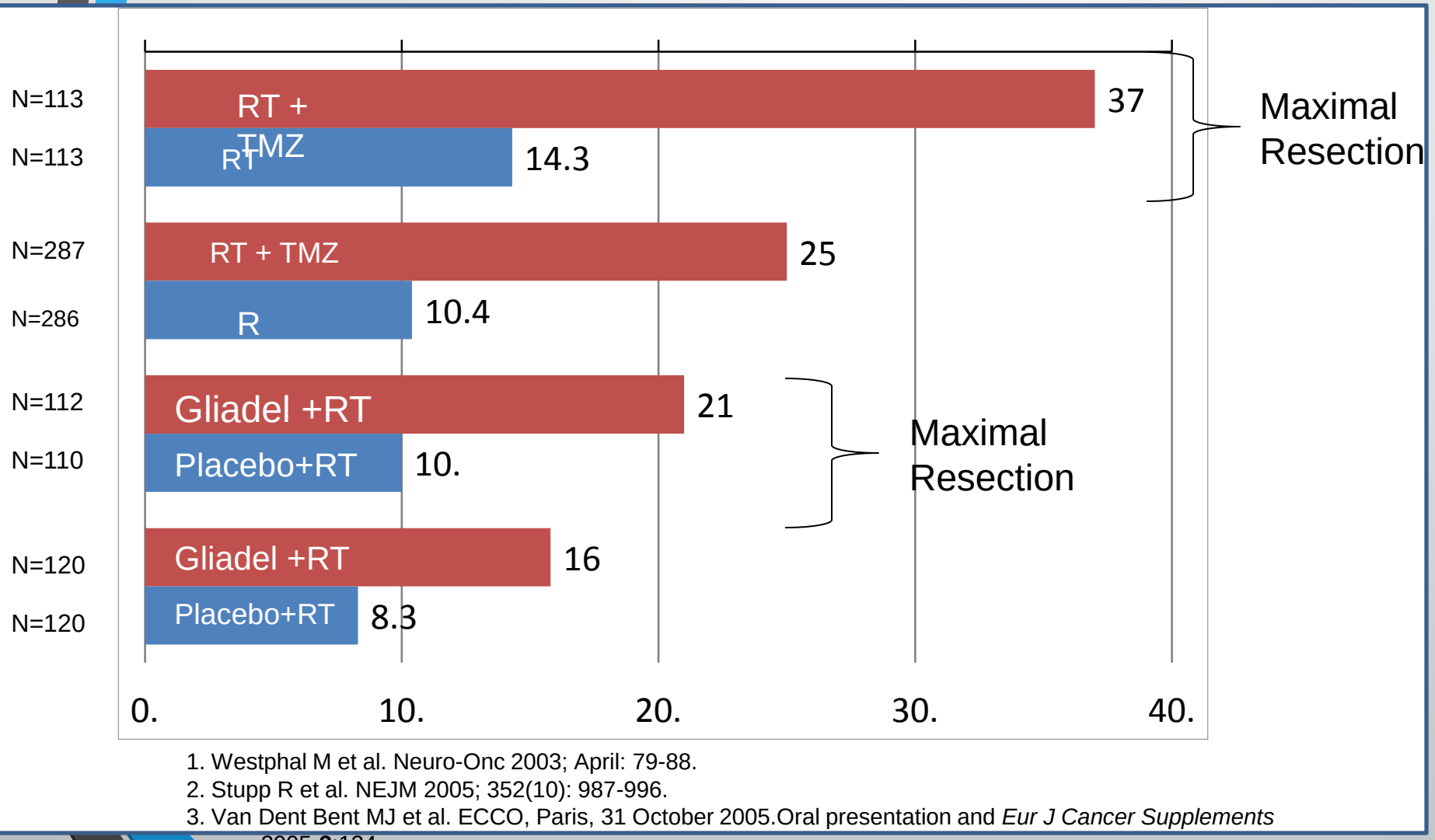
What is the Tumour Load?



How much removal gives benefit>> 75% ->95% of what ?

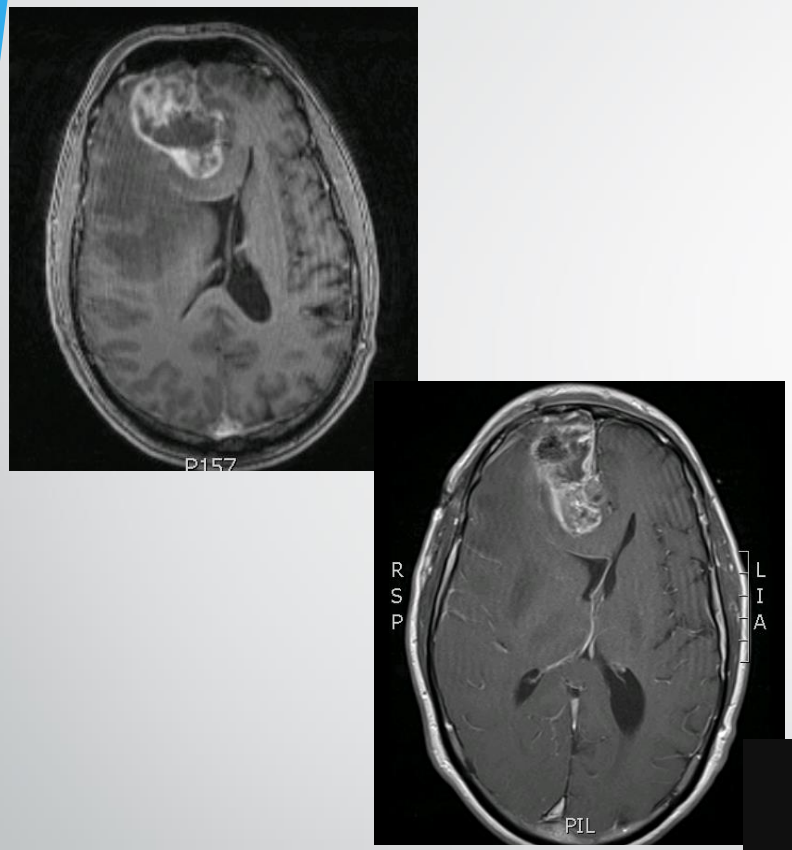
GBM:Results Summary

2yr Survival (%)



1. Westphal M et al. Neuro-Onc 2003; April: 79-88.
2. Stupp R et al. NEJM 2005; 352(10): 987-996.
3. Van Dent Bent MJ et al. ECCO, Paris, 31 October 2005.Oral presentation and *Eur J Cancer Supplements* 2005**;3**:134

Incomplete removal> brain swelling



54 yr old man with
R. Frontal GBM

1st Op "v. Vascular"

Poor recovery with further deterioration at 24hrs

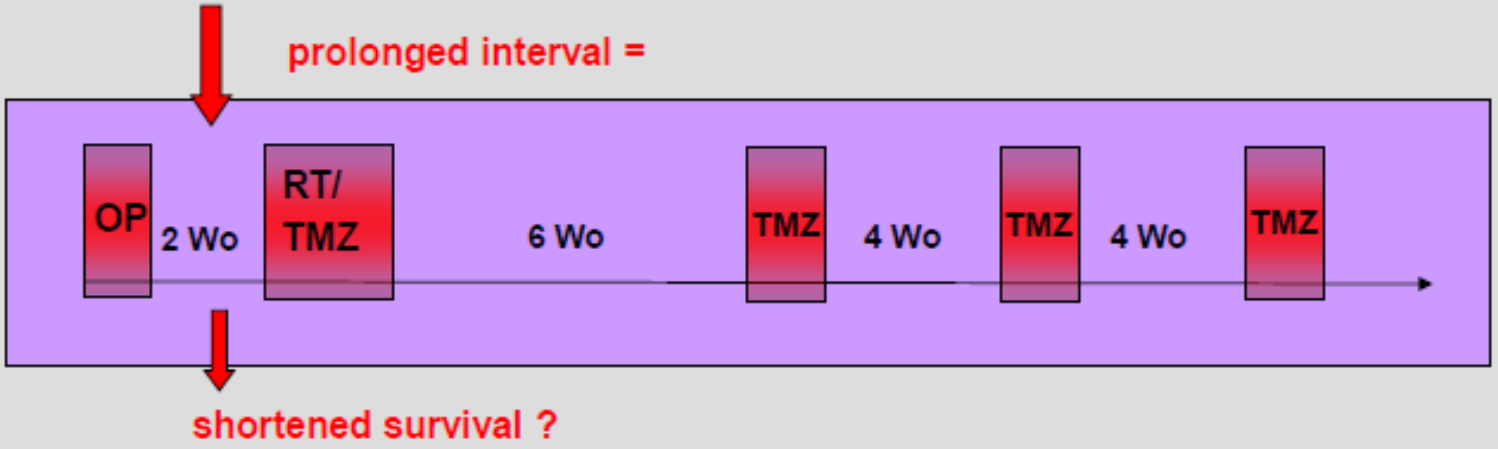
MRI worse brain oedema

2nd Operation required

Surgical Risk of Glioblastoma Resection

major complications: 8.9%

- 12/243 severe hemiparesis (4.9%)
- 3/243 severe aphasia (1.2%)
- 6/243 hemiplegia (2.4%)
- 1/243 mono-paresis (0.4%)



Stummer, Tonn et al. 2011

My Conclusions –

1. Gross total resection is the desired aim if it can be done safely

2. BUT we do NOT know the total tumour load so we can never be sure as to the actual resection success --this explains why it is so difficult to prove survival benefit or
? future improvements in survival from surgery

3. New techniques make it possible to standardise a better resection (5ALA and Mapping)

4. But what happens next is determined NOT by what has been removed
eg genetics, epigenetics etc but by what is left behind and we know next to nothing about this and how it changes after resection and treatment

5. Most of our patients receive adjuvant therapy and the evidence would suggest that this works better with good resections

Biological consequences of Resective Surgery of Gliomas

- Fewer tumour cells
  ↑ chance of sustained immune control
  ↑ response to chemotherapy (gliadel)
- Reduced Hypoxia ie normoxia
  ↑ number of cells sensitive to RT
- Reduced Oedema/ mass effect
  ↓ need for steroids ↑ sensitivity to treatments
- Microenvironmental Change
  ↑ local release of growth factors →number of cells 'in cycle' (Ki67/PCNA)BUT ↑ chemo/radiation sensitivity

Surgical Strategy – malignant glioma

- Patients with **„resectable“ glioma**

  → microsurgical resection

- Patients with nonresectable glioma / glioma in eloquent area ***without mass shift***

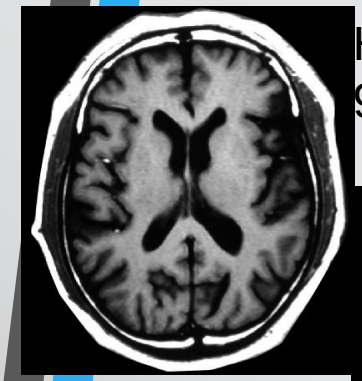
  → biopsy including molecular signature

- Patients with only partially resectable glioma (parts of tumor in eloquent area) ***and mass shift***

  → partial resection to allow additional radio- & chemotherapy

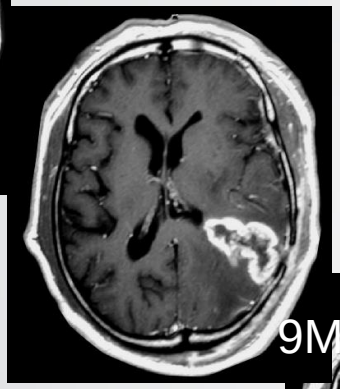
  avoid additional surgical morbidity !

Glioblastoma - Clinical Course



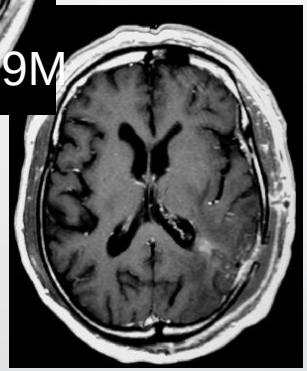
Head trauma
9M before

50% of patients Only



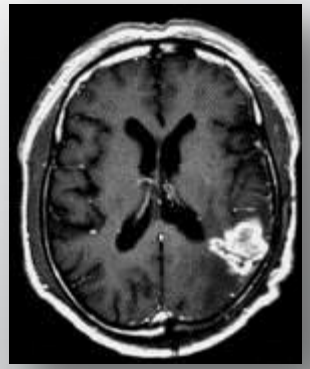
Mild headache

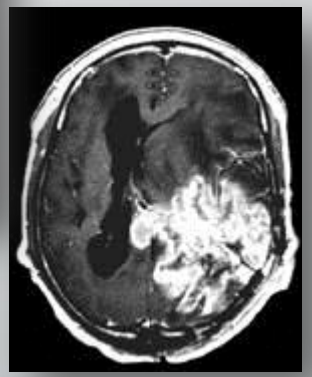
Post-surgery



9M

Post-chemo-radiotherapy





Surgery >>

Radiation>>

Chemotherapy

1. Only Half get any Improvement with Temozolomide
2. All will have recurrence of their tumours

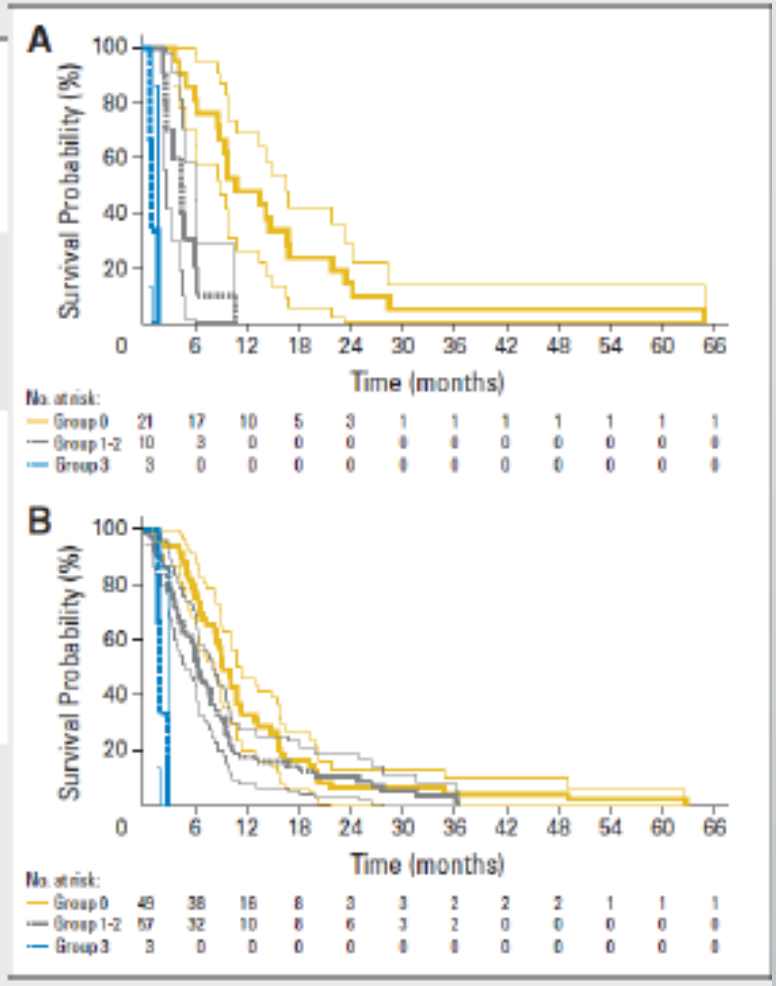
Scale to predict survival after surgery for recurrent glioblastoma multiforme

Park JK et al., J Clin Oncol. 2010; 28:3838

Table 3. NIH Recurrent GBM Scale

Cohort and Score	Median Survival (months)	95% CI	Prognostic Group
NIH			
0	10.8	8.9 to 16.7	Good
1-2	4.5	2.7 to 6.1	Intermediate
3	1.0	0.9 to 1.1	Poor
BWH			
0	9.2	8.2 to 11.3	Good
1-2	6.3	4.8 to 7.9	Intermediate
3	1.9	1.7 to 2.9	Poor

Abbreviations: NIH, National Institutes of Health; GBM, glioblastoma multiforme; BWH, Brigham and Women's Hospital.



Scale to predict survival after surgery for recurrent glioblastoma multiforme

Park JK et al., J Clin Oncol. 2010; 28:3838

Table 2. Univariate Analysis of Prognostic Factors

Factor	Median Survival (months) Yes	No	*P*
No. of eloquent/critical regions, ≥ 2*	1.4	9.0	< .001†
KPS, ≤ 80*	2.5	9.6	< .001†
Tumor volume, ≥ 50 cm^3*	3.9	10.3	< .001†
Predominantly frontal lobe tumor	6.2	9.7	.227
Time from initial diagnosis*, ≥ 6 months	7.4	8.5	.236
Corticosteroid use	6.1	9.8	.349
Relationship status, married	8.6	6.0	.459
Headaches	7.9	7.3	.543
Seizures	9.7	6.1	.714
Sex, female	7.9	7.4	.802
Age*, > 50 years	6.1	8.6	.823
Tumor side, left	7.4	7.5	.825

Abbreviation: KPS, Karnofsky performance status.
*Values were dichotomized to yield greatest hazard ratios.
†Included in multivariate analysis.

NB: Recurrent surgery for GBM is much riskier !

Detect any recurrency early to maintain options for additional therapy !

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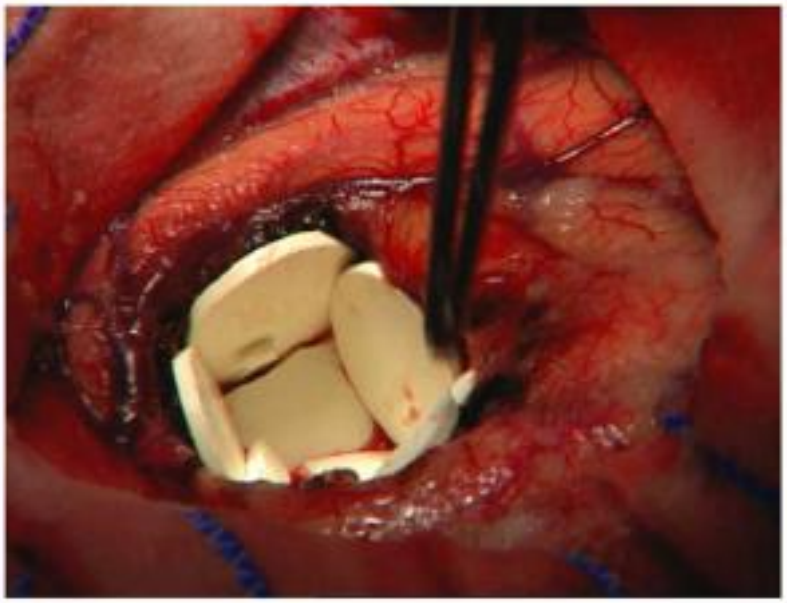
Park JK et al., J Clin Oncol. 2010; 28:3838

If you can detect early recurrence by doing 2 monthly MRI scans you will be able to offer early treatment AND access to Clinical Trials

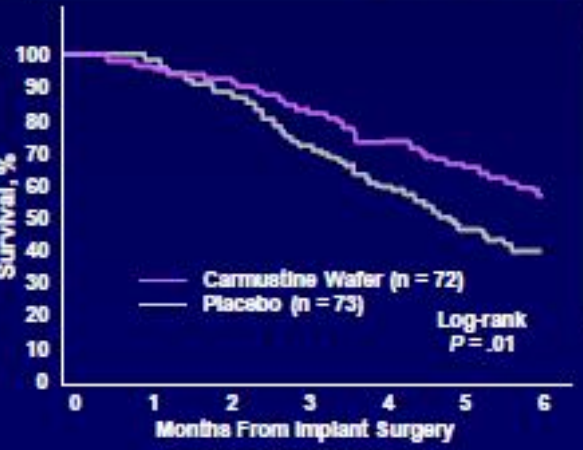
Surgery for Recurrent GBM

Few studies addressed the benefit of resection at recurrence as the sole therapy



Nature Reviews | Drug Discovery

	Carmustine wafer (n = 72)	Placebo (n = 73)	*P* value
6 month survival rate	56%	36%	.013
Median OS (95% CI)	6.51 months (5.32, 7.49)	4.63 months (3.78, 5.52)	.181



Carmustine wafer-treated patients with GBM demonstrated a 56% survival rate at 6 months compared to 36% in the placebo

Brem H, et al. *Lancet.* 1995;345(8956):1008-1012.

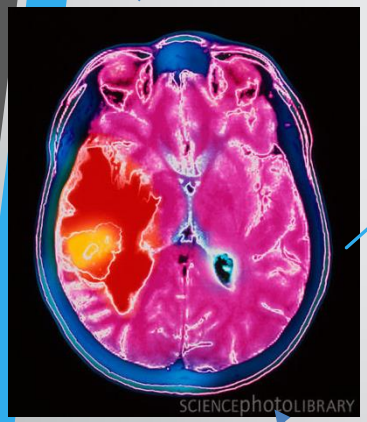
Future Neurosurgery

1. Improved resection- 5ALA + , iKnife
2. Tumour Staging –Gene expression
3. Tumour for Immuno- therapy- DCVax
4. Window Studies- Neo adjuvant drug selection
5. Drug delivery – Depot therapies, Convection Enhanced Delivery
6. Enhanced Drug delivery- US, MRI
7. In Situ RT - Holmium nanospheres
8. In Situ Electrical Therapy - electrode placement
9. Neurosurgical Robots
10. Surgeon Monitoring -

Dendritic Cell Therapy:

Tumour sample
From patient

Tumour Protein/Antigens isolated



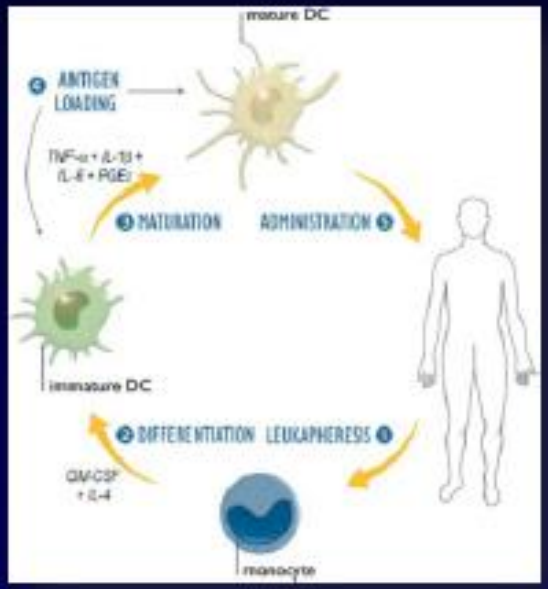
Dendritic Cells
Isolated

Dendritic Cells activated
by exposure to orignal tumour protein

Activated Dendritic
Cells grown

Repeated SC Vaccination of patient
Activated Dendritic
cells

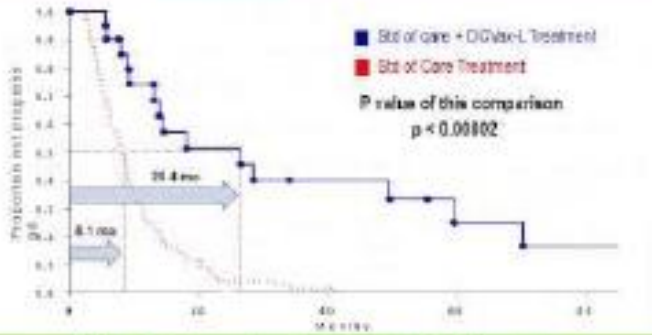
DC Vax Study



DCVax®: The Process

1. Blood taken from patient
2. dendritic precursor cells separated out
3. dendritic cells develop in lab
30 days
4. DCs exposed to cancer protein in flask, "teaching" the DCs to recognize the antigen
5. "Educated" DCs injected back into patient: they "teach" the immune system to fight the cancer

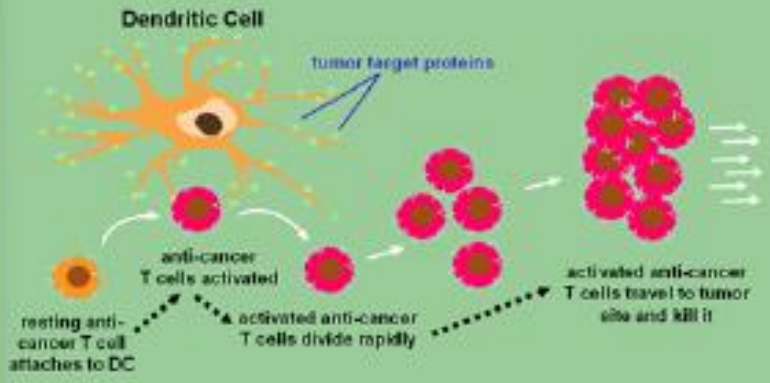
DCVax®-L in Newly Diagnosed GBM: Progression Free Survival (PFS) in Phase I/II Trials

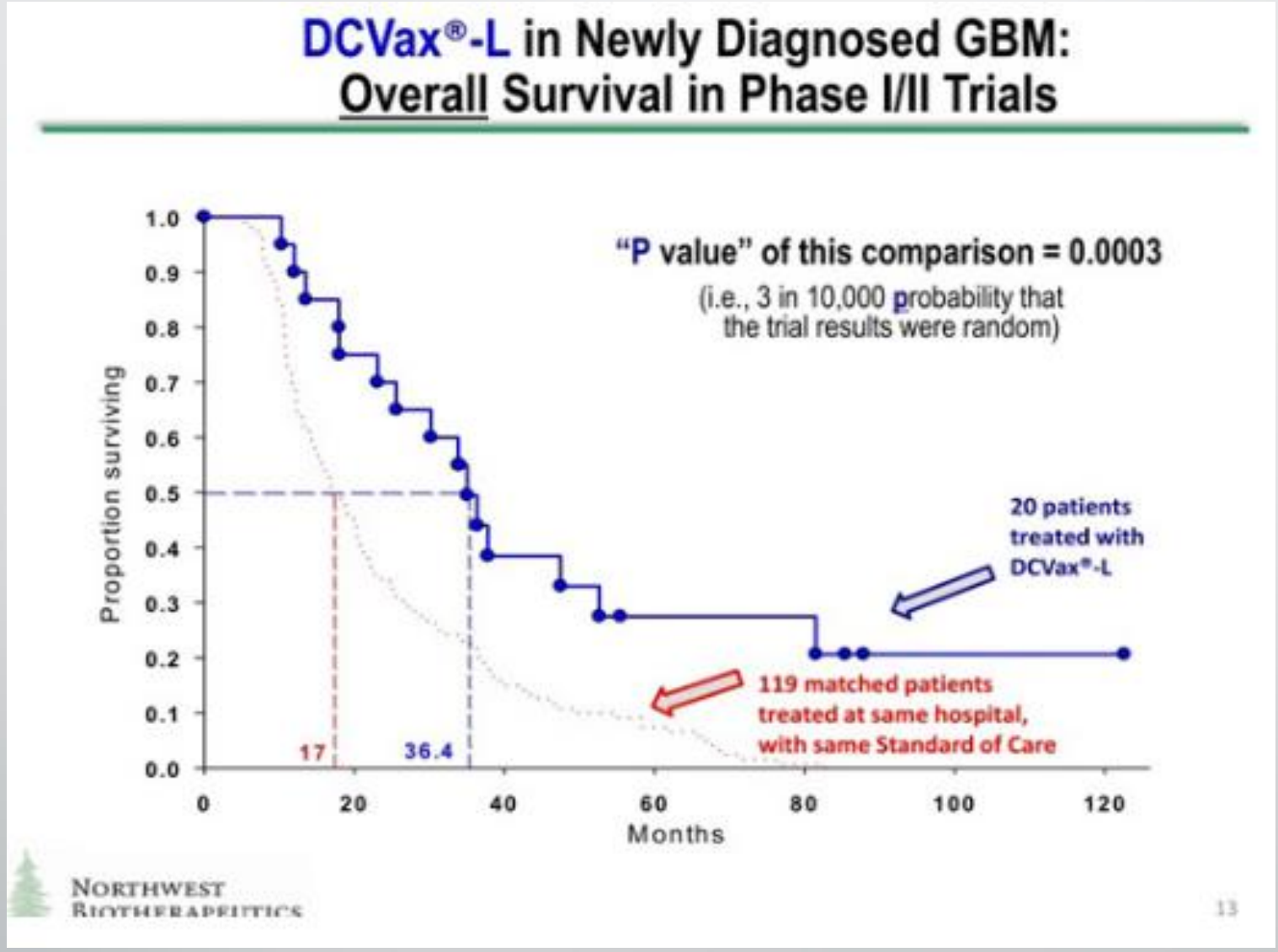


DCVax®-L showed an 18.3 month PFS benefit over standard of care in newly diagnosed GBM patients

NORTHWEST BIOTHERAPEUTICS

One "Educated" Dendritic Cell Activates Hundreds of Anti-Cancer Cells





"there is a probability of 0.0356% that the 20 patients that received the DCVax vaccine had no increased survival due to the vaccine " –independent reviewer

Drug/Agent Delivery

Depot therapy

Convection Enhanced

Delivery Enhanced -US/ blood brain barrier manipulation

Drug Eluting Beads

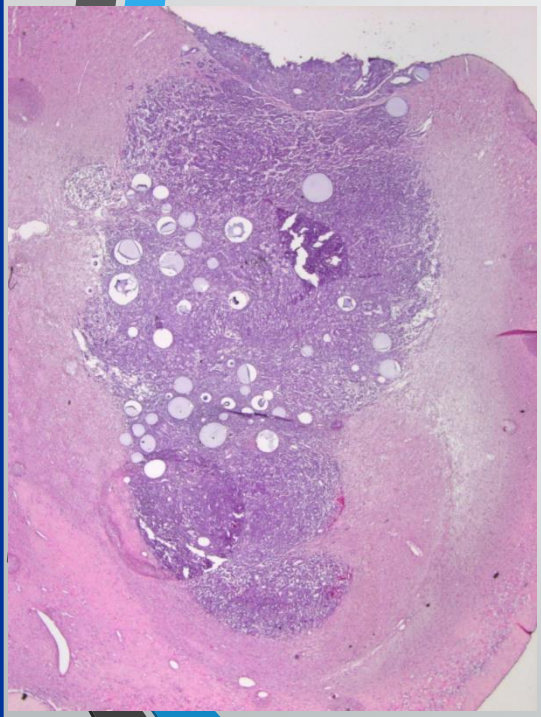
Irinotecan from drug eluting beads (IDEB Biocompatibles & UoB)

Post resection depot therapy in recurrent GBM - Phase 1

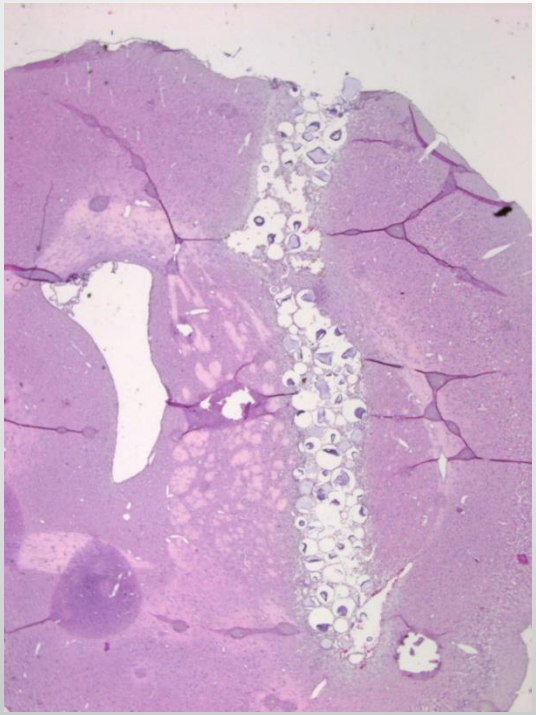
Irinotecan DEB Anti-tumour Activity

Drug Eluting Beads

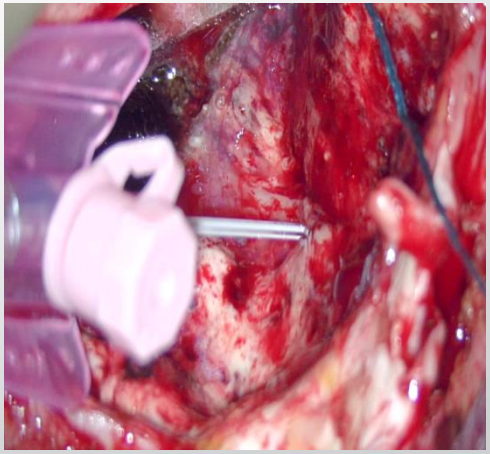
Tumour volume at day 15



Unloaded Beads



Irinotecan DEB



Phase 1 Recurrent GBM :
Injection of
post resection cavity wall
(SNO2015)

Sapphire CED Delivery System

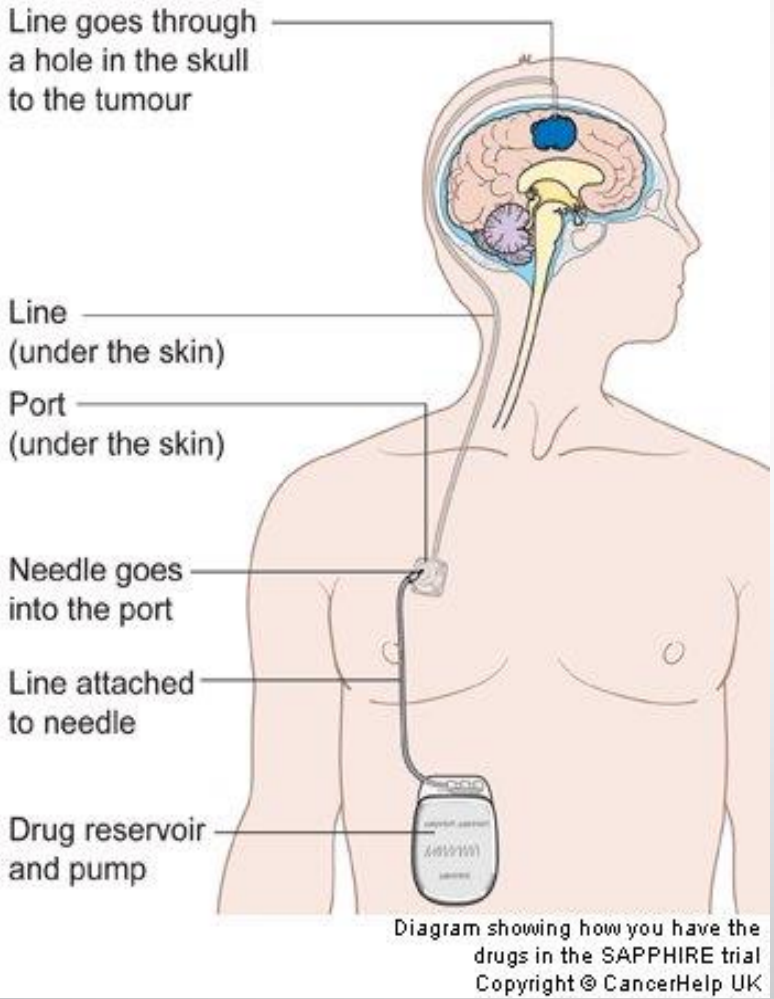
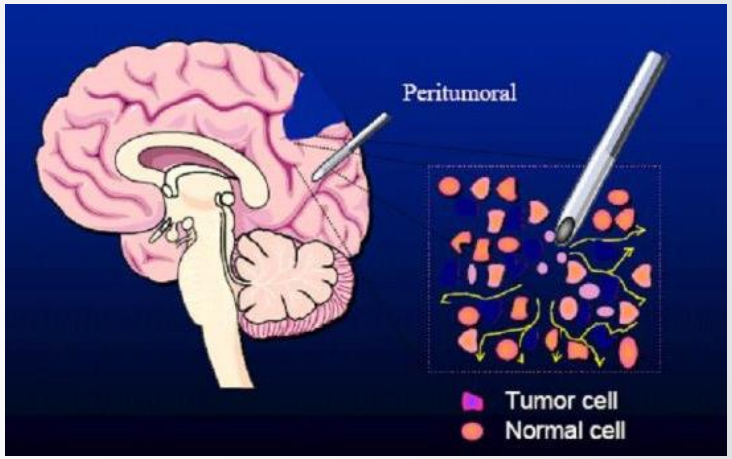
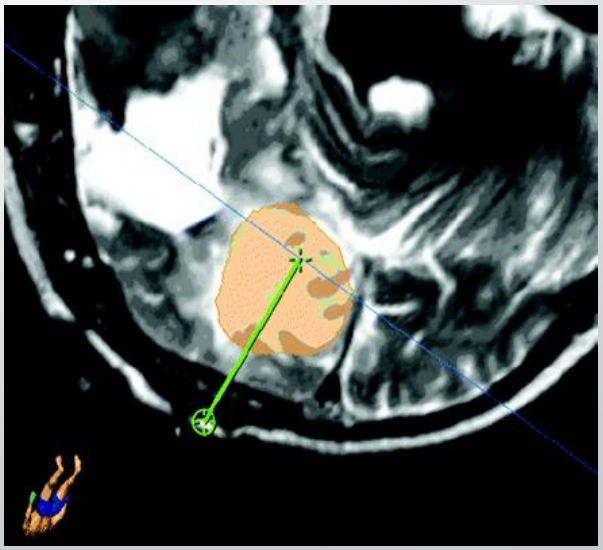


Diagram showing how you have the drugs in the SAPPHIRE trial
Copyright © CancerHelp UK

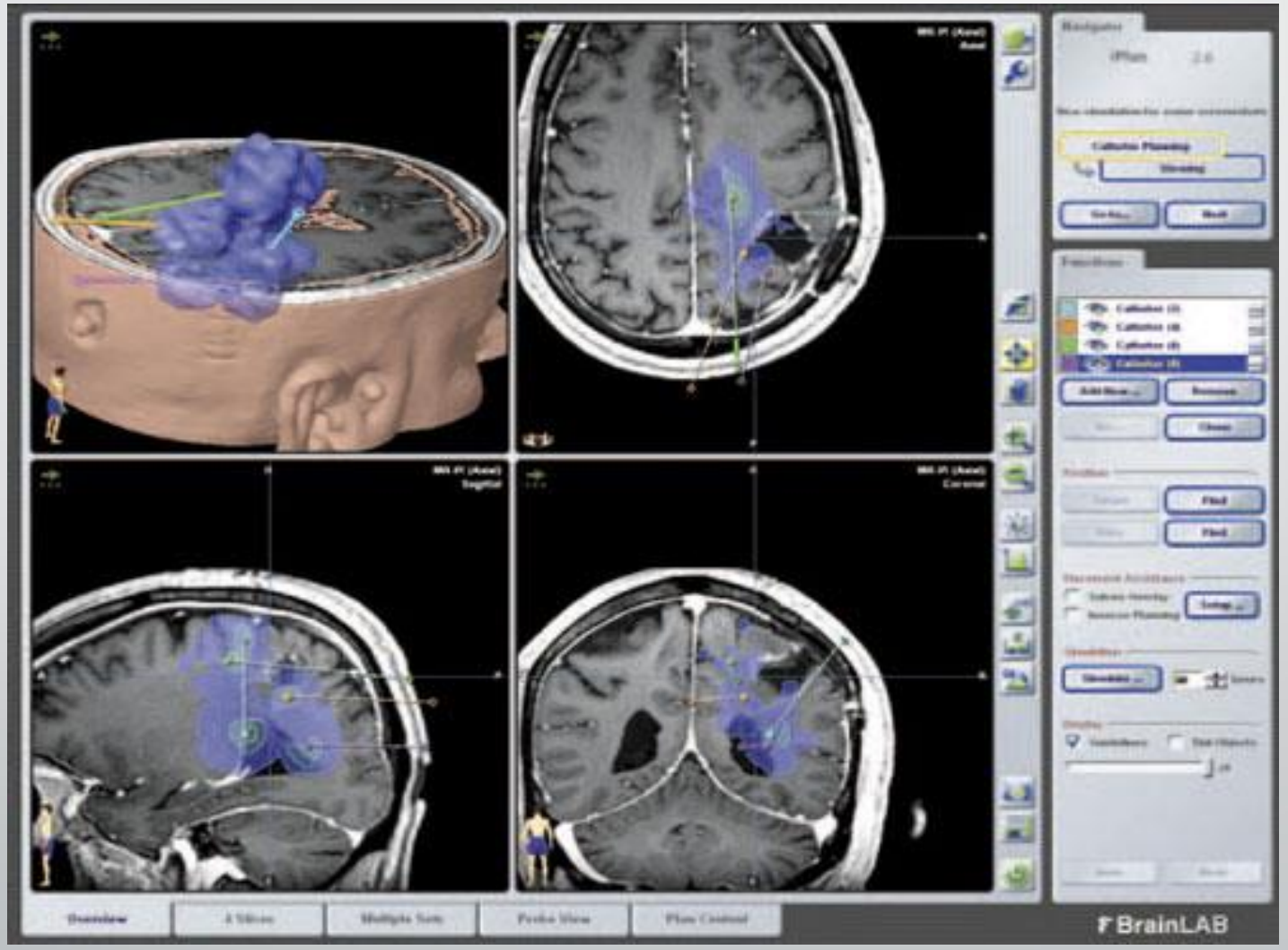




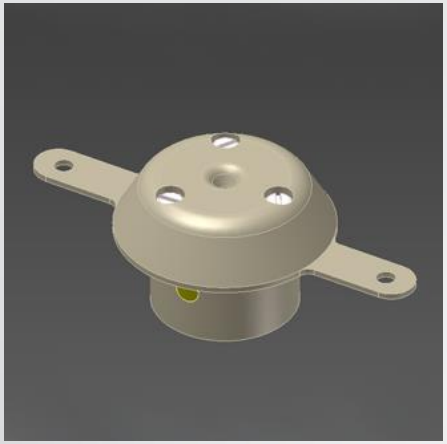
SAPPHIRE trial

- TGFbeta2 is a cytokine whose production is upregulated in glioma
- It is intensely locally immunosuppressant
- Impairment of TGFbeta production might enable antigen presentation to work effectively and enable long term control of disease
- TGFbeta antisense (Trabedersen) can be given by intermittent Convection Enhanced Delivery via implanted catheters.

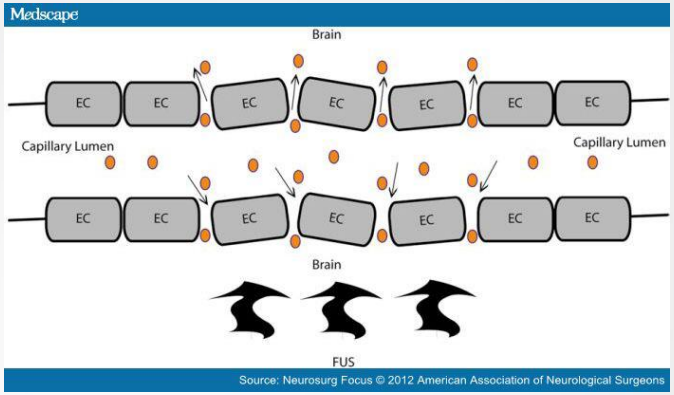
Planning CED delivery volumes

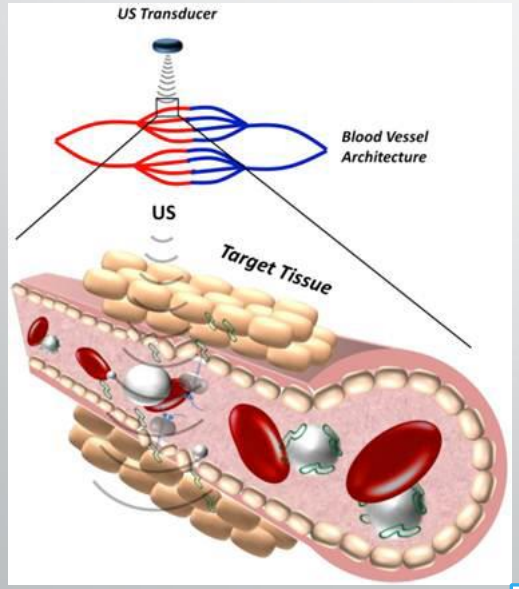


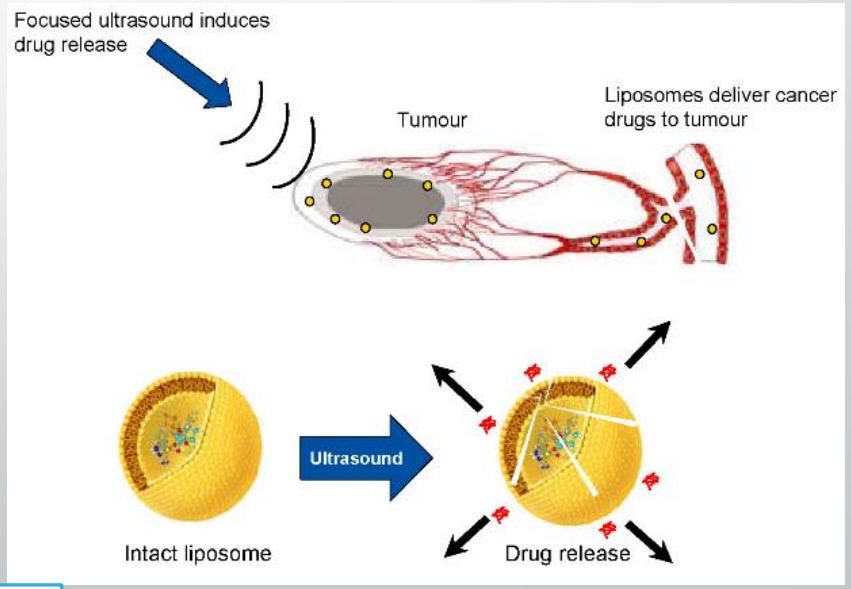
Focused Ultrasound



Burr hole insert US Probe







Enhanced Surgery

Reoperation

Extent of Resection-

Extended Resection-Endoscopic

Robotics

iKnife

Electrocautery 'smoke' extracted to intraoperative M as Spectrometer
Mass Spectrometer Profile used to characterise a tiss ue type
Signal back to Surgeon

? Resolution of probe
? Calibration of system

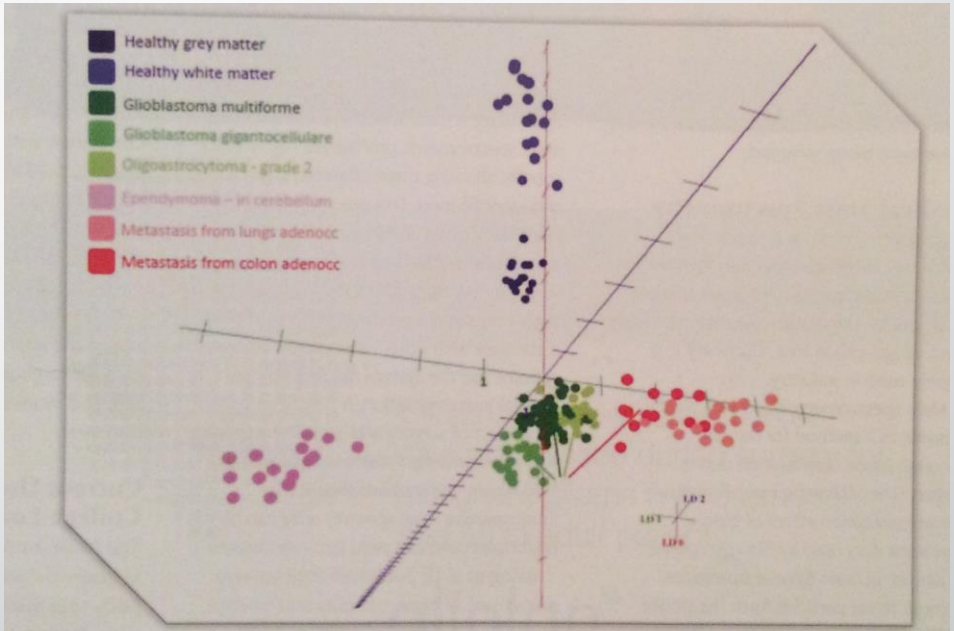
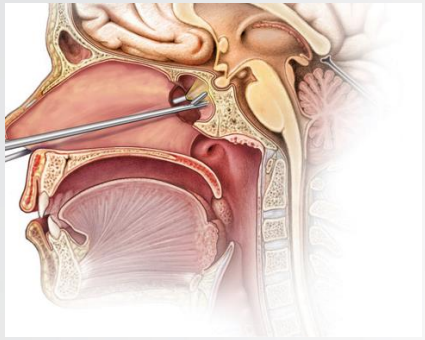
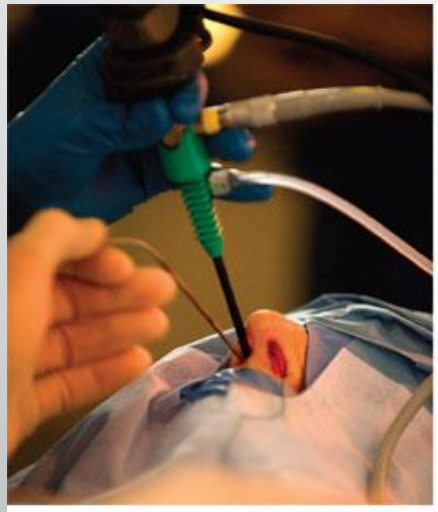


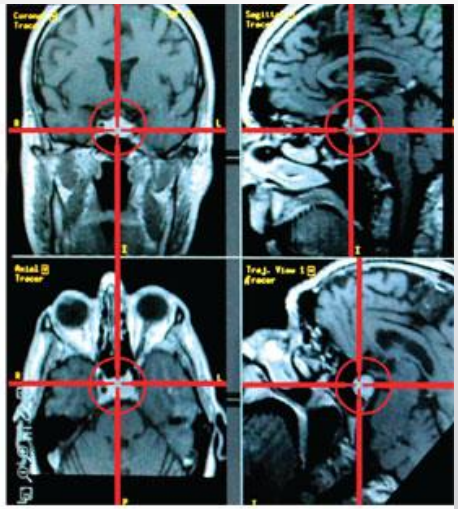
Figure 1 Mass Spectral Analysis on a Principle Component Analysis plot showing separation of different tissue types.

Endoscopic Tumour Resection

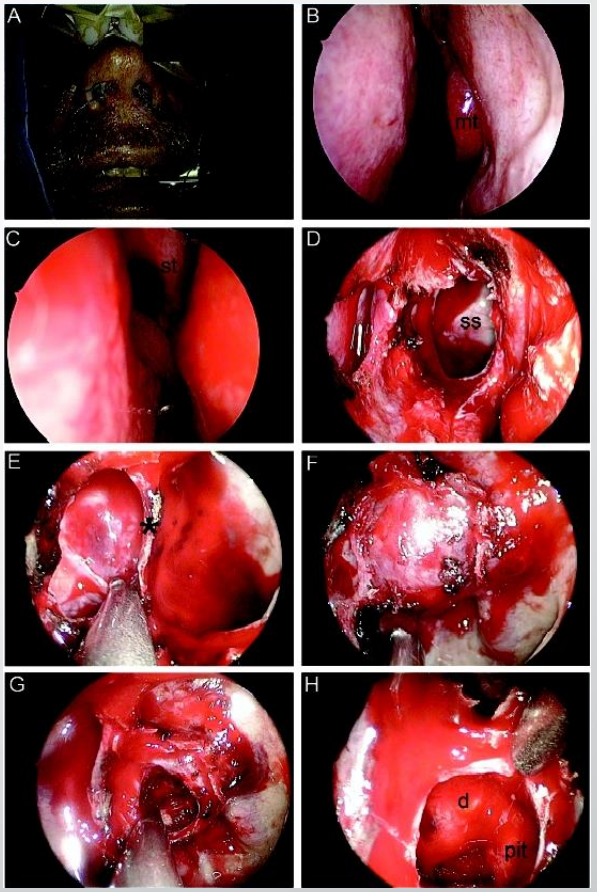




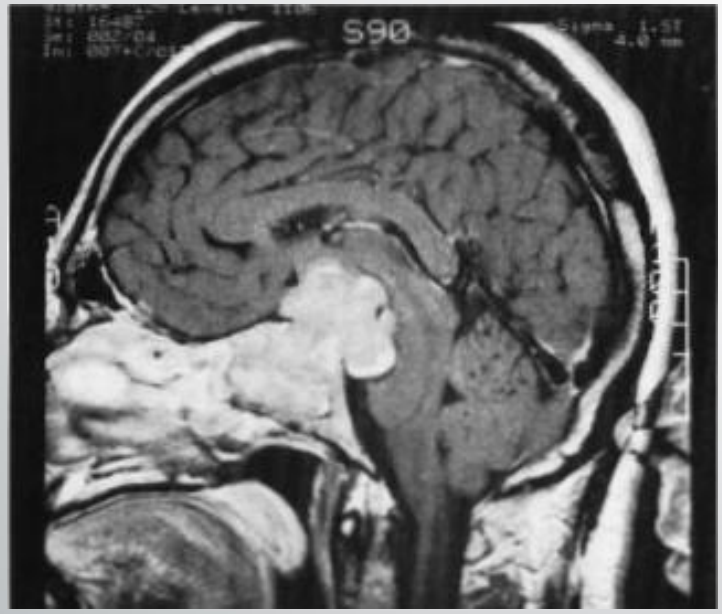
Endoscopic resection of pituitary tumor through the nose

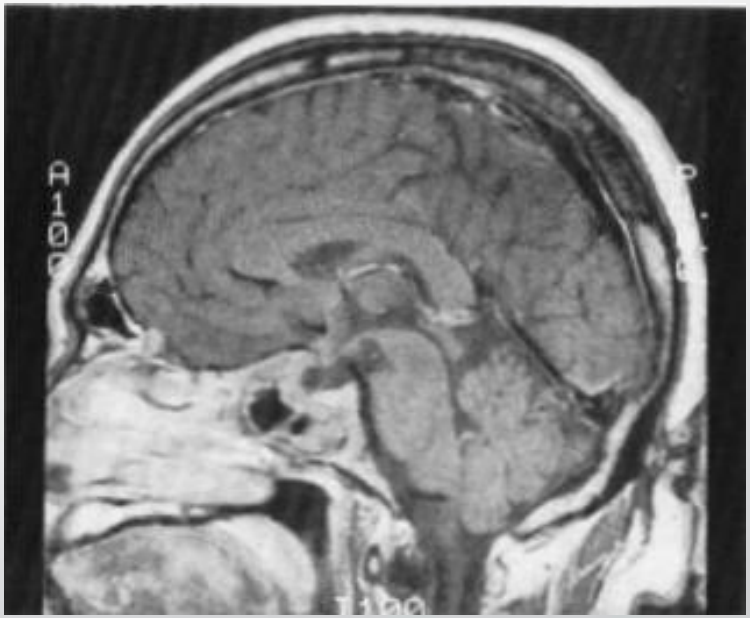


Computer image guidance system



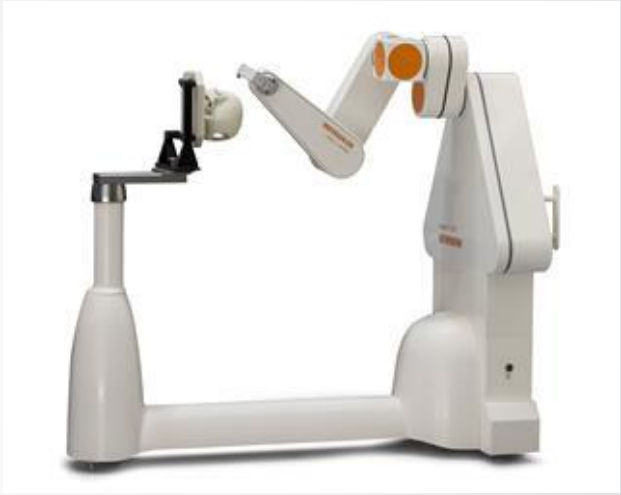
Results

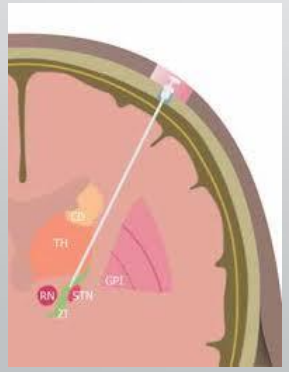


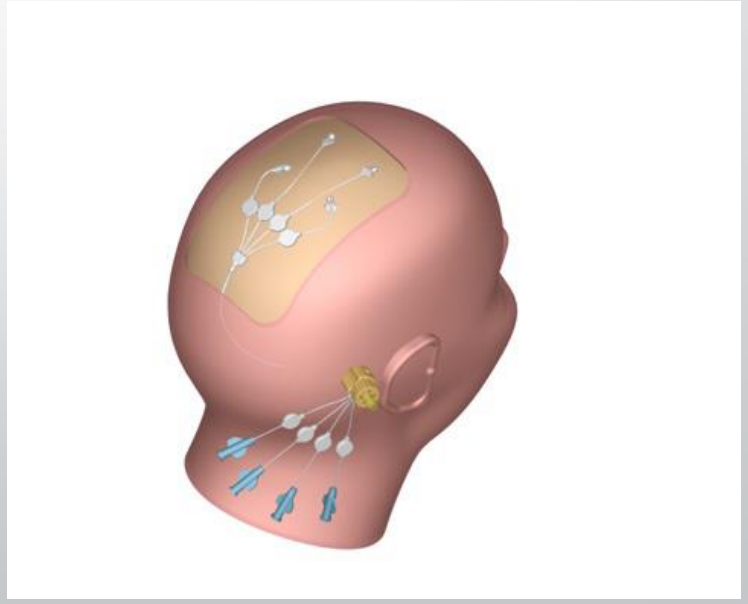


Robotics

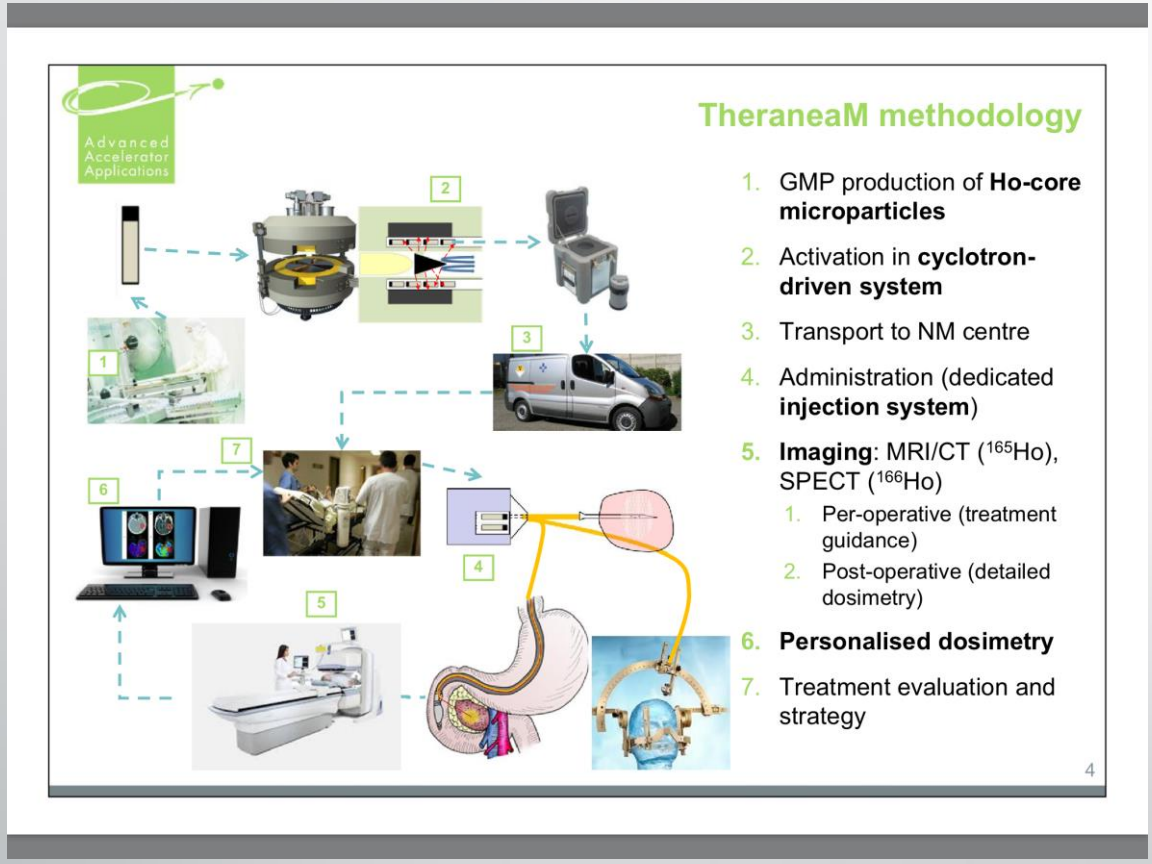
Implantation
- Electrodes
- CED catheters
- Depot Drug rods

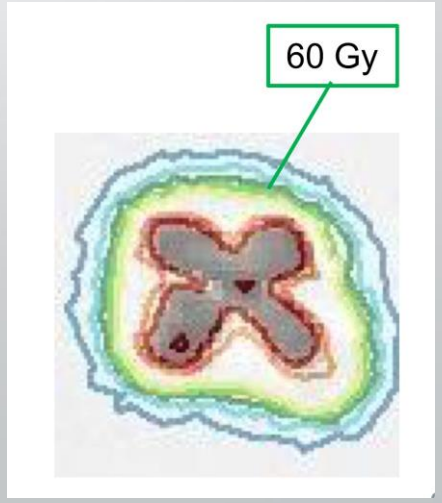




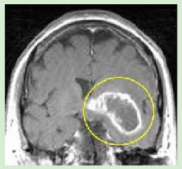
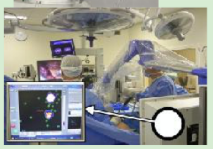


InSitu Radiotherapy

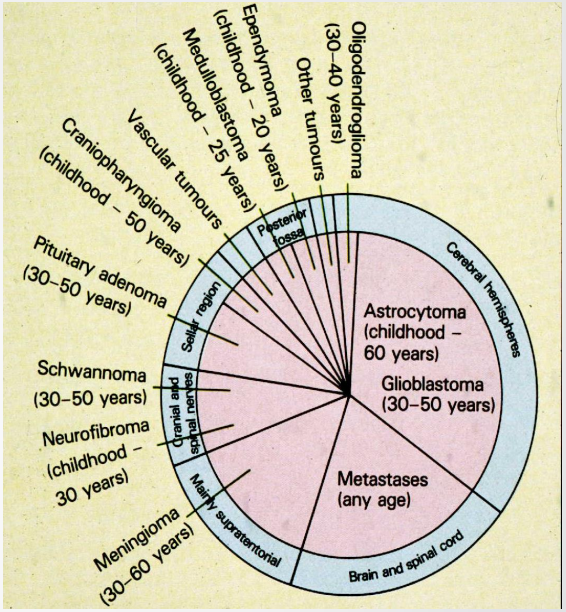




TheraneaM-IT TPP: clinical procedure (glioblastoma)

Item	Description	Comments
Pre-operative operations	• Accurate morphological analysis/stereotactic modelling (MRI, CT) • Assessment of tumoral tissue characteristics • Estimation of injection protocol based on injector performance database (planning software)	
Needle positioning	• Stereotactic needle positioning ✓ Either manual or with robotic arm ✓ More than one hole could be foreseen for better tumour accessibility	
Per-operative Imaging	• Visualisation of Ho distribution at each injection step by (as available) MRI, portable CT and γ-camera ✓ Real-time (preliminary) dosimetric calculation ✓ Adaptation of the procedure to the results	
Post-operative Imaging and dosimetry	• MRI/SPECT-CT acquisition and multimodality dosimetric calculation • Assessment of obtained dosimetry and decision on treatment repetition	
Treatment repetition	No basic limitations for repeating the treatment in case of unsatisfactory result or relapse	

Metastases Origin



- Lung- Half of cases
- Breast
- Melanoma-highest incidence of any Cancer 40-60% (50-70y)
- Renal cell
- Colorectal

- Other!

Surgical Resection

- Confirms Histology ---markers/epigenomes
- Rapid symptom control
- Allows steroid reduction
- Large Tumours

- vs
- Invasive
- Morbidity (<5%) vs site of lesion
- Techniques en bloc vs piecemeal vs recurrence
- Selective Surgery and WBRT may be best for symptom and survival*
- Added risks eg DVT in patients who have had much chemotherapy before.
- Median Survival 8-16mths local recurrence 7-15%

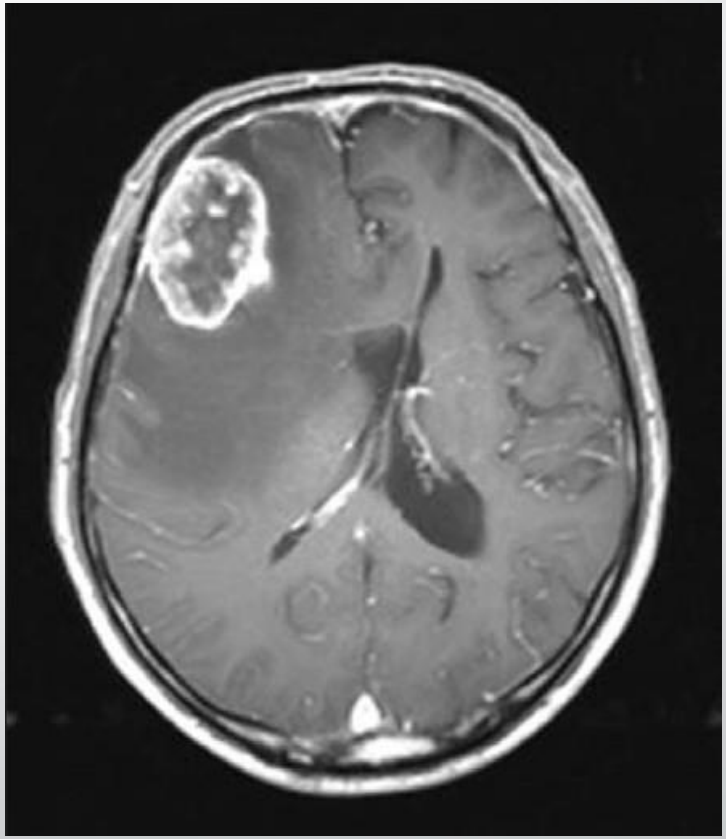
* Phase III RCT *Patchell et al 1998 JAMA 280:1485-1489* local and
* distant recurrence lowest

Metastases Imaging

- MRI 50-80% Multiple
- Breast vs Renal

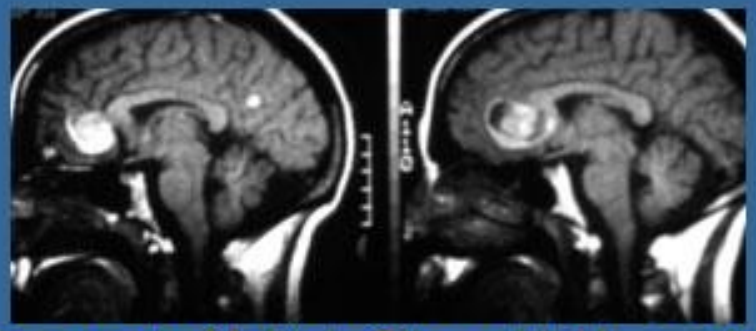
- Well Demarcated- but infiltration* ?
- Enhancing (T1 + Gd)
- Junction of Grey/White
- Cerebrum/cerebellum /brain stem 80/15/5
- Excess Oedema

* cv Glioma

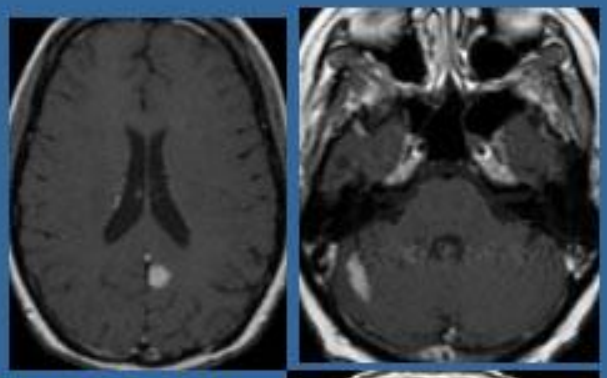


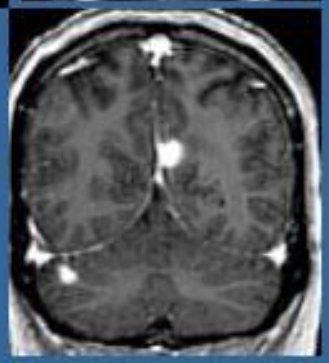
Metastatic Brain Tumors

Brain metastases occur in 10-30% of cancer patients and are seen most commonly in patients with lung, breast, melanoma, colon, renal or thyroid cancers. The MRIs below show 3 different patients with metastatic tumors from melanoma, breast and renal cell carcinoma.

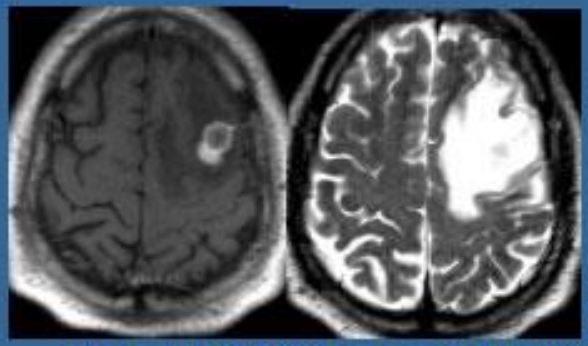


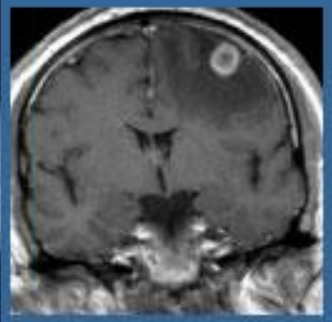
Melanoma to Multiple Sites with Hemorrhage





Breast Cancer to Left Occipital Lobe and Right Cerebellum





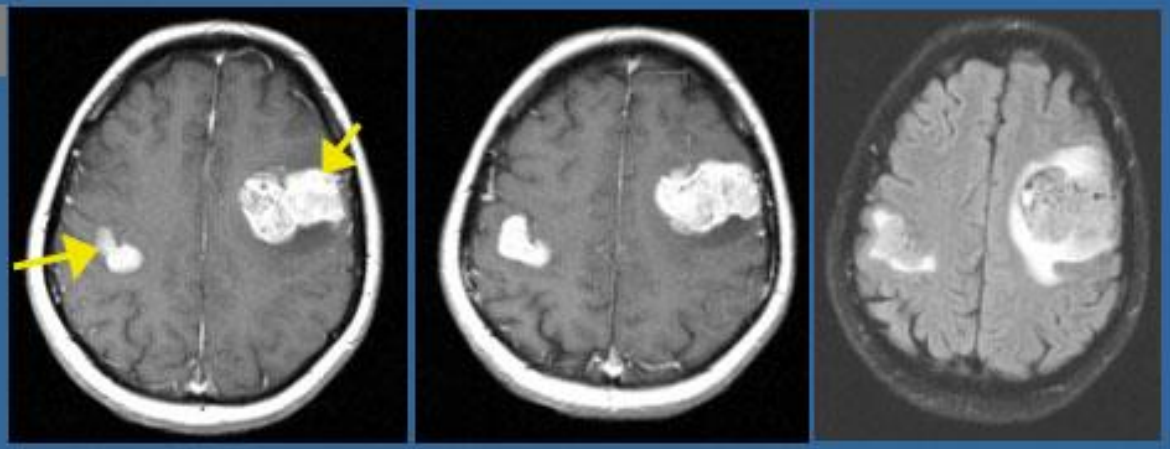
Renal Cell Cancer to Left Frontal Lobe Causing Severe Brain Edema

Metastatic Melanoma

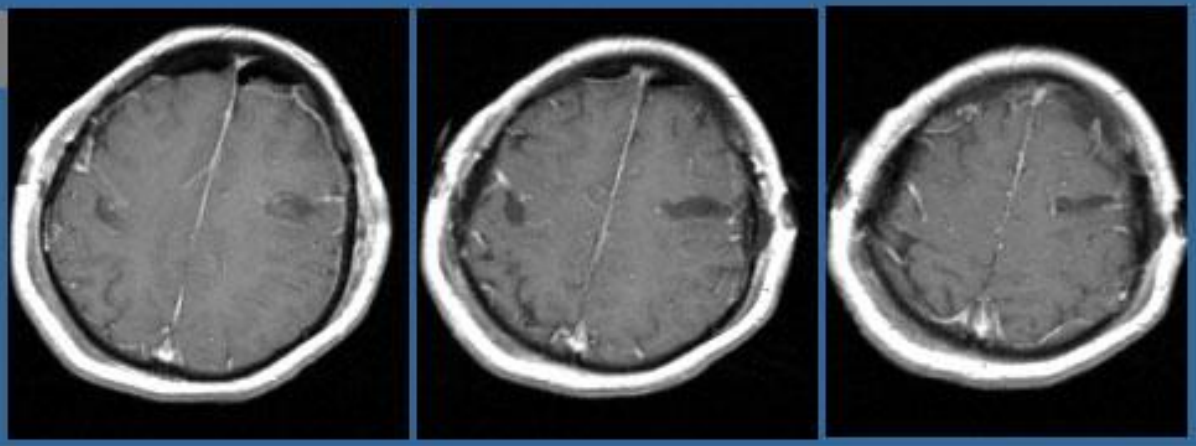
A 43 year-old woman developed two large metastatic melanomas to the right & left hemispheres despite chemotherapy and radiotherapy.

Both tumors were completely removed using surgical navigation through 2 small craniotomies. She has done well after surgery and continues treatment with chemotherapy.

Pre-op



1 Day Post-op

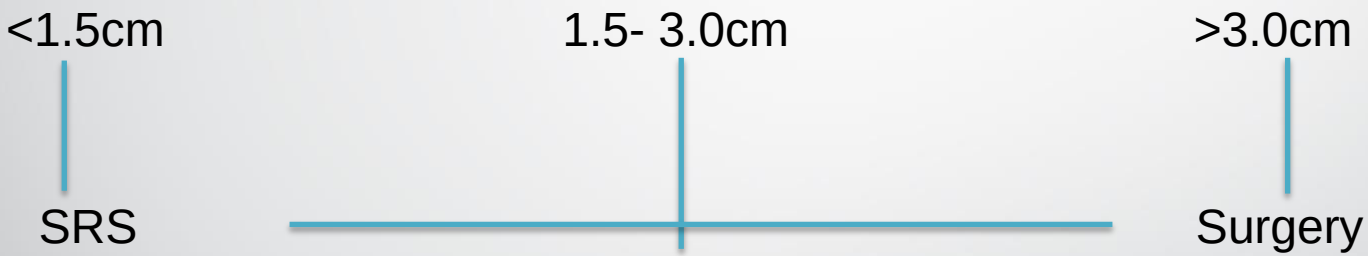


Current Practise

- Recent tendency to avoid WBRT eg Breast Ca where survival >1yr expected for single brain met.
- Local or recurrent Mets could then be treated surgically or SRS
- NB: Need 2/12 imaging for one year.
- Still needs RCT for evidence

Management Plan

Metastasis



Clinical Status
-patient
-Tumour RT response
- Neuro Status

What is a Neurosurgeon

- First Point of Contact
- First to deliver 'Bad News'
- Technical Expert
- Disease Expert
- Team Player
- Team Leader
- Team Headliner

NeuroOncology Surgeon UK

- Spends >50% of Surgical Time on brain tumours
- Full attendance at >66% of weekly Multidisciplinary Meetings
- Carries out weekly Specialist Clinics in eg Glioma, Low Grades, Skull Base etc
- Undergoes Annual Peer review (Web View)
- Undergoes annual appraisal and surgical audit

How am I doing?

National Neurosurgical Audit

iNeurosurgery

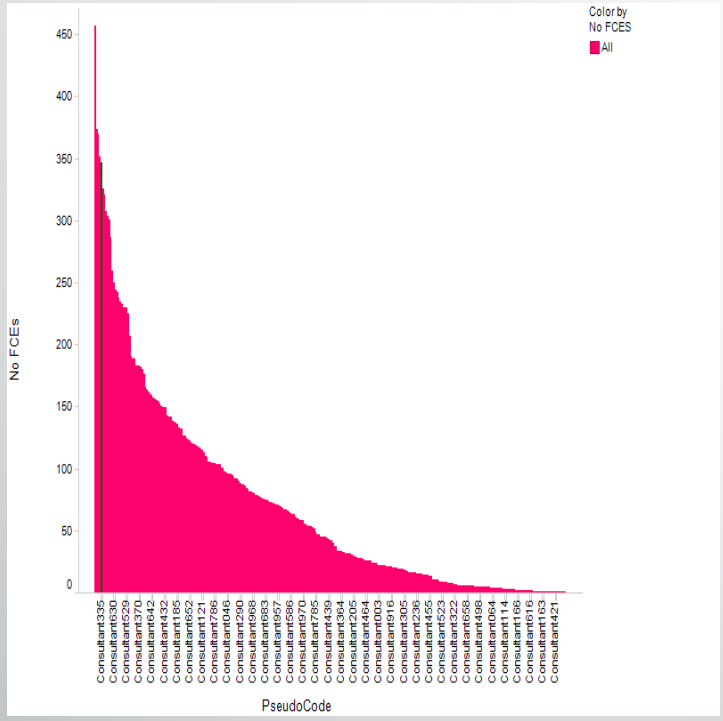
Surgeon Reported Outcomes

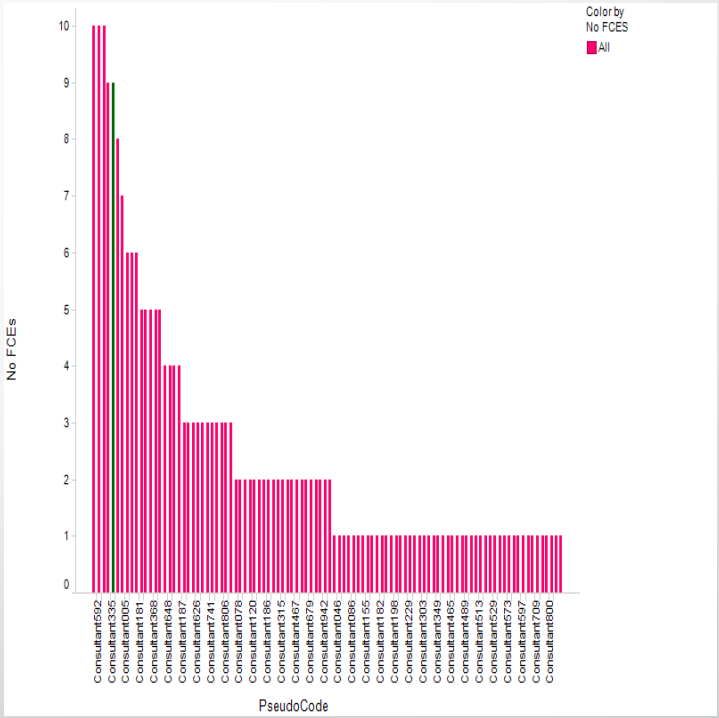
Areas of Measurement

- Numbers of operations
- Numbers of deaths
- Numbers morbidity
- Numbers of unexpected morbidity
- Numbers related to surgeon error

FCE's: A02 and A02 + C71 F

Normalised Y axis values





= ~200 cases pa

Acceptable? Mortality and Morbidity-intrinsic brain tumours

Mortality 1.7 – 2.7% (30d)

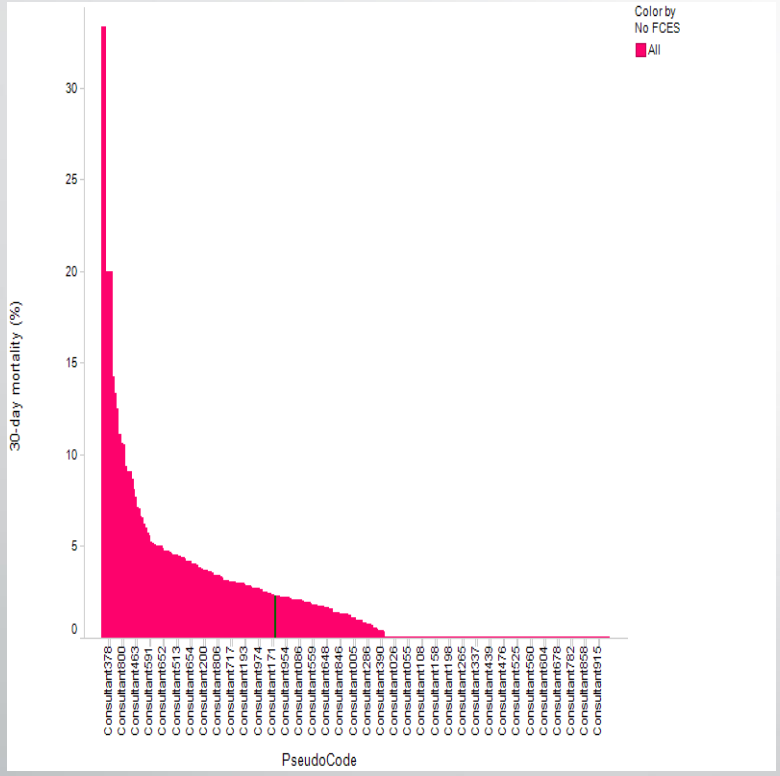
Sawaya R, Hammond M, Schoppa, D et al Neurosurgical outcomes in a modern series of 400 craniotomies for treatmentof parenchymal tumours
Neurosurgery 1998 42 1044-1055
Stone S, Bernstein M Prospective error recording in surgery: an analysis of 1108 elective
neurosurgical cases Neurosurgery 2007 60:1075-1080

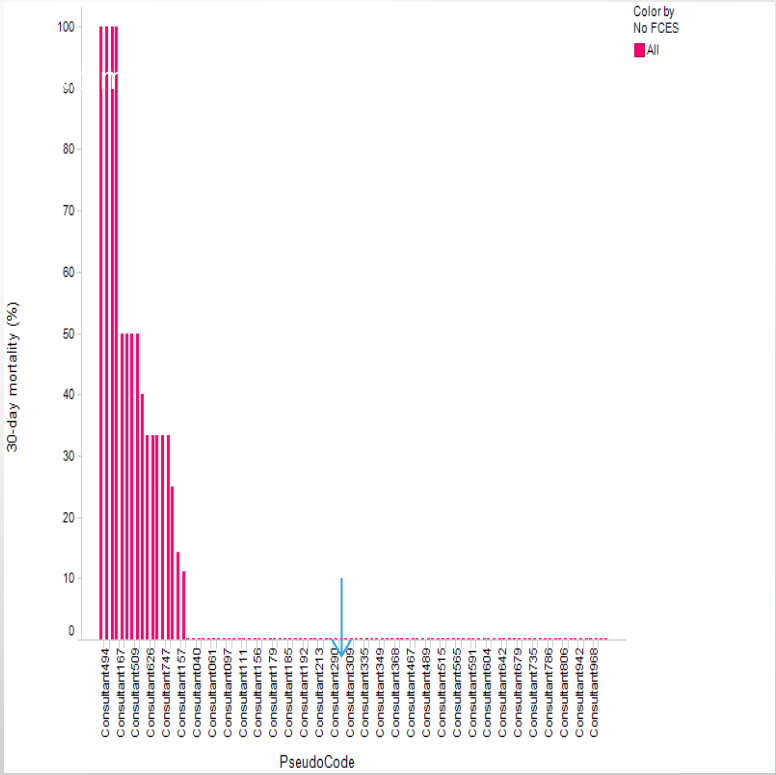
Morbidity – surgical 5-8% for low comorbidity cases.

-medical 5-10%

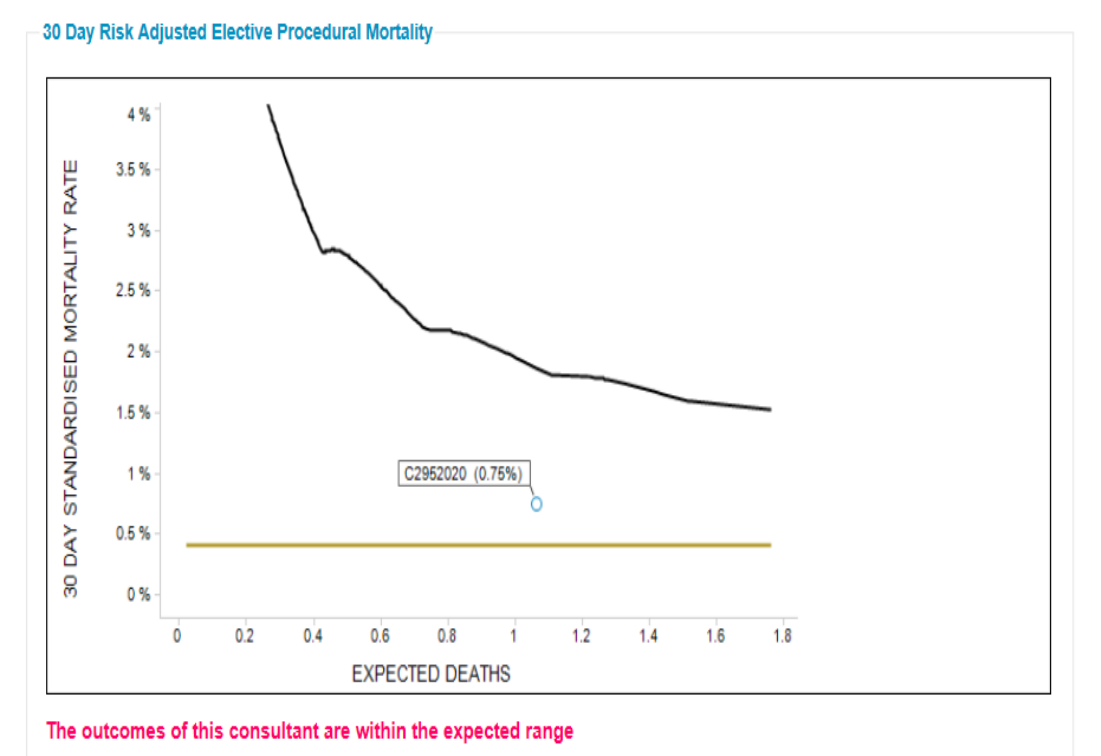
Wong J, Panchmatia J, Ziewacz J
Patterns in neurosurgical adverse events : intracranial neoplasm surgery
NeuroSurgical Focus 2012 33: E16

30day Mortality:
A02 and A02 + C71 (ie GBM)





Funnel Plot


30 Day Risk Adjusted Elective Procedural Mortality
30 DAY STANDARDISED MORTALITY RATE
4 %
3.5 %
3 %
2.5 %
2 %
1.5 %
1 %
0.5 %
0 %
C2952020 (0.75%)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
EXPECTED DEATHS
The outcomes of this consultant are within the expected range

Thanks to you and My team