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Current and future challenges in glioblastoma tretment

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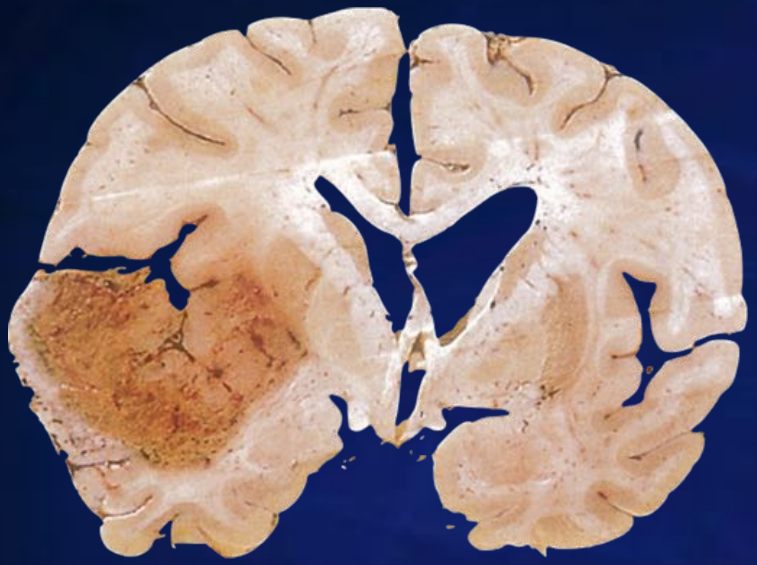
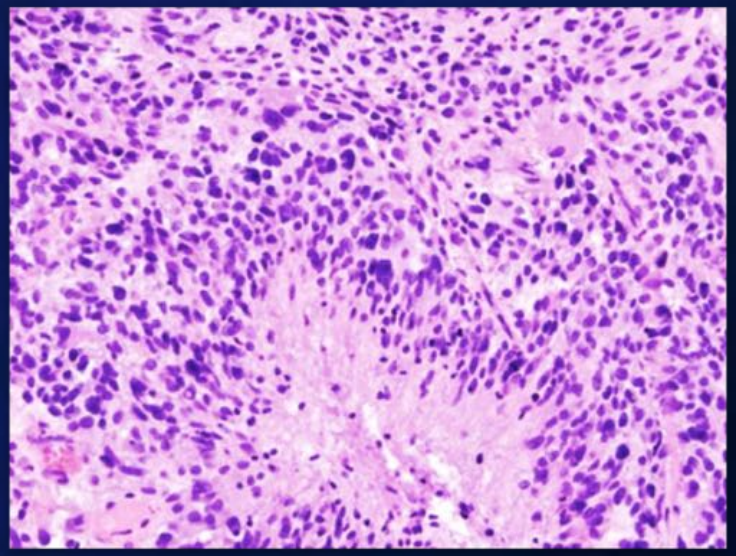
Switzerland
Chairman: Prof. Andreas Raabe

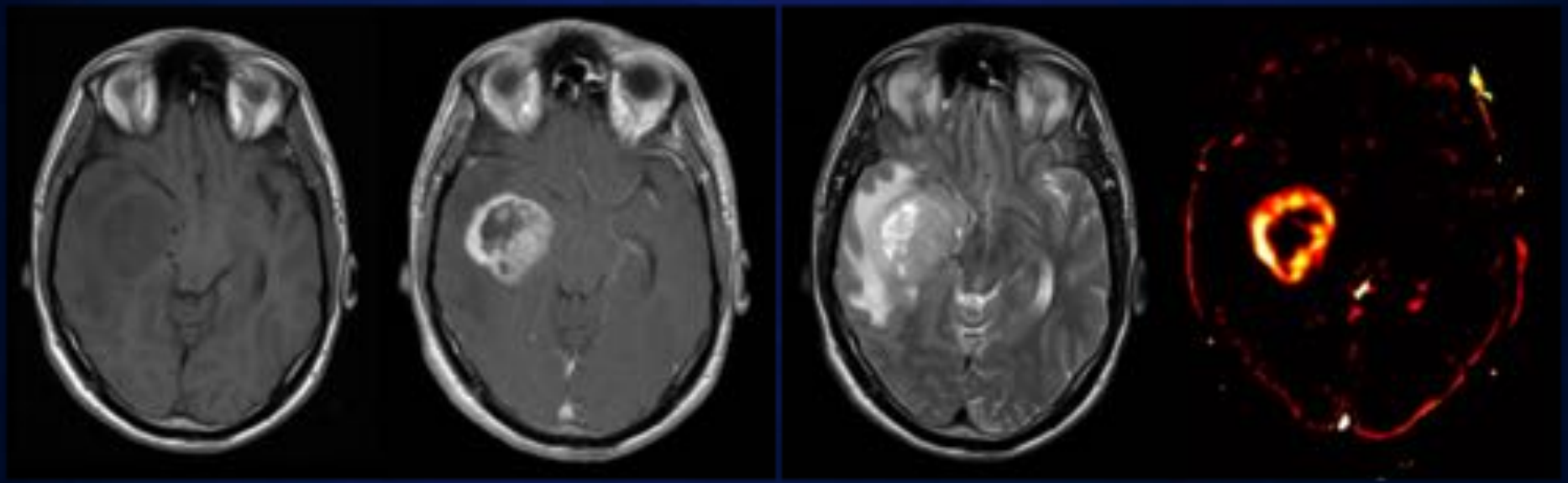
Glioblastoma WHO° IV



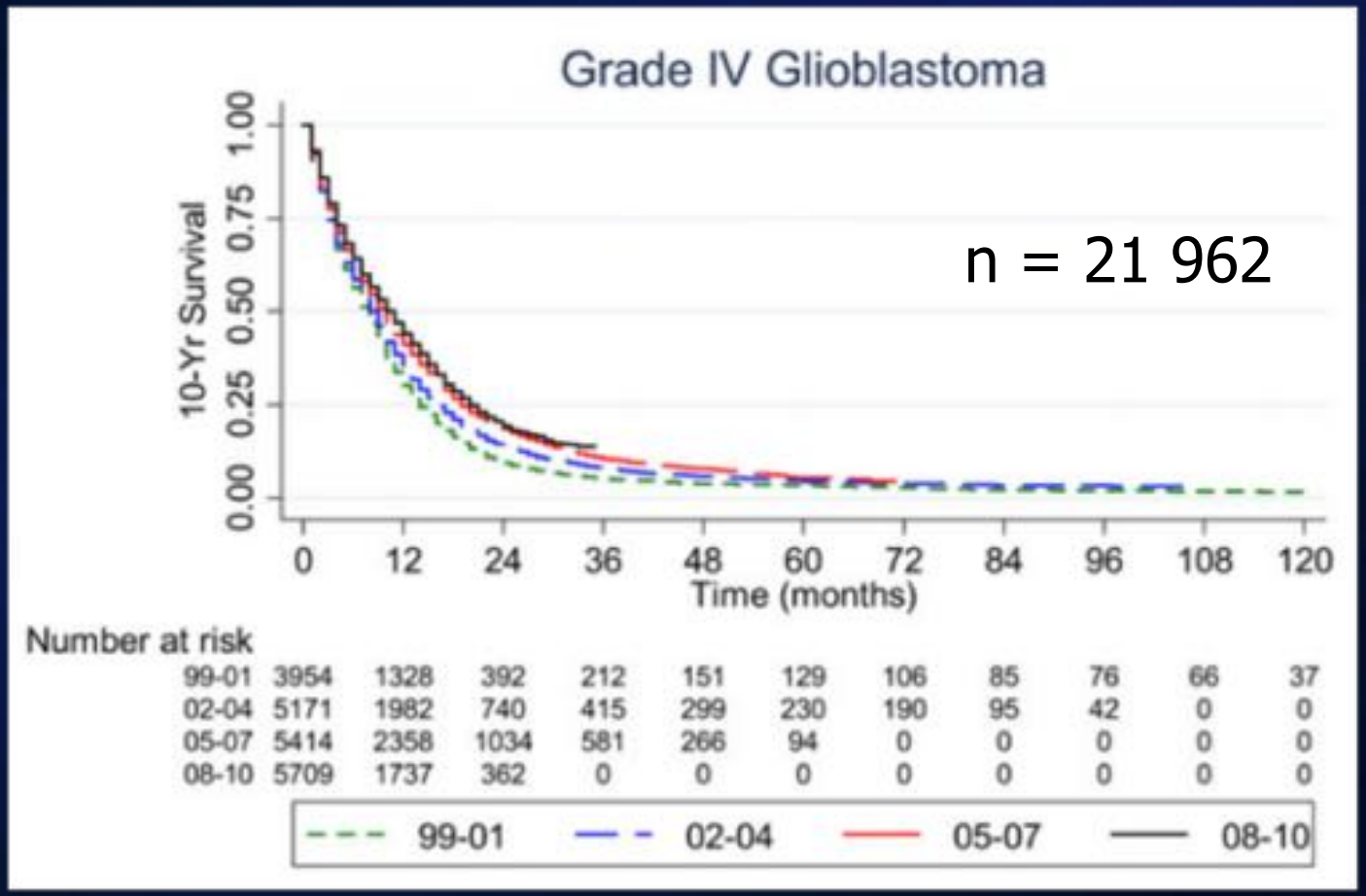


- The most common primary brain tumor, also the most malignant astrocytoma
- Most GBMs arise de novo (primary), others progress from less malignant astrocytomas (secondary)
- Primary GBM: more common in older Patients (mean age = 55years) after a short (< 3 month) history
- Secondary GBM: develop by malignant degeneration of WHO ° II and ° III astrocytomas (mean age = 40 years)

Glioblstoma on MRI

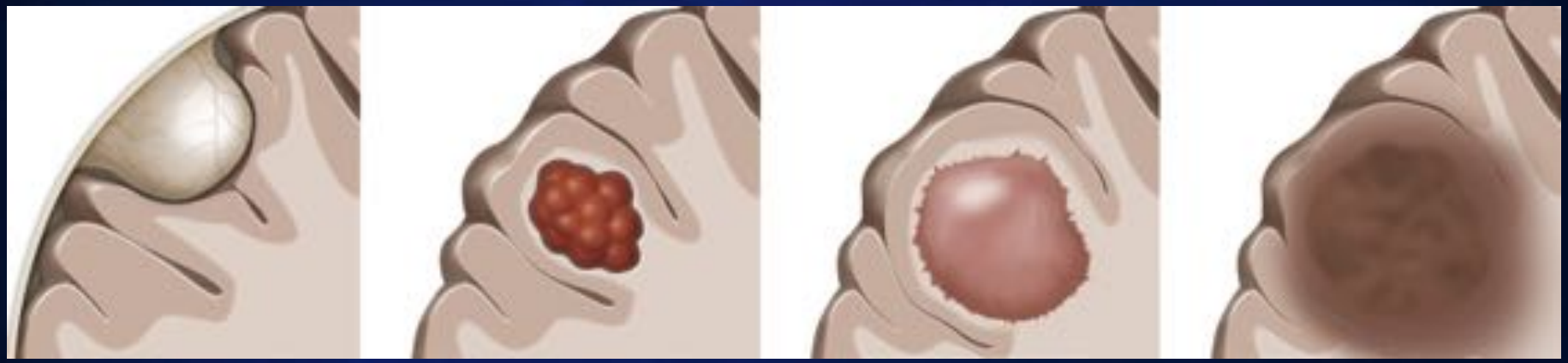


Survival



Survival trends of grade I, II, and III astrocytoma patients and associated clinical practice patterns between 1999 and 2010: A SEER-based analysis
Xuezhi Dong et al., Neuro-Oncology Practice 3(1), 29–38, 2016

Sharp regular border	Sharp irregular border	Small Infiltrative border	Large Infiltrative border



Meningioma	Cavernoma	Metastasis	Astrocytoma, GBM

Risk of white matter tract or cortical injury

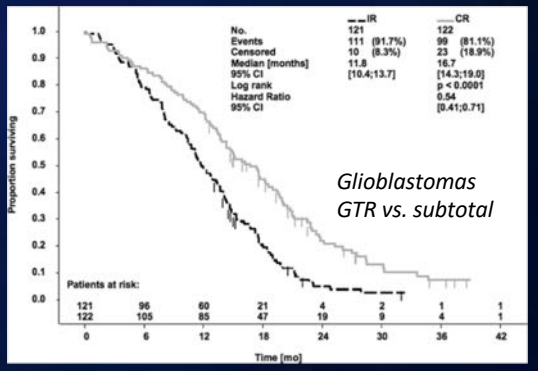
Challenge:
to investigate the effect of different surgical resection concepts on survival

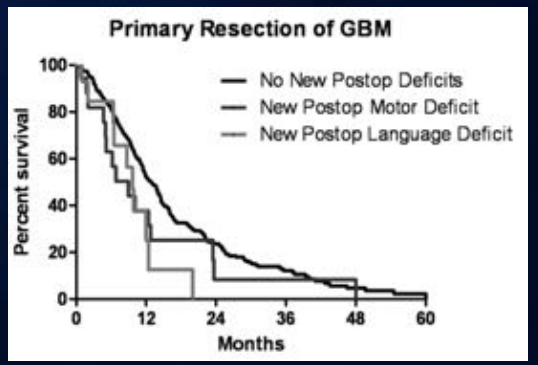
The current dogma of glioma surgery
Maximum safe resection

1. Infiltrative gliomas: no cure by surgery

2. Extent of resection correlates with survival *Lacroix et al. JNS 2001; Sanai and Berger Neurosurgery 2008; Sanai et al. JNS 2011; Stummer et al. Lancet Oncol 2006; Smith et al. J Clin Oncol 2008; Salvati et al. JNS 2012*

3. New permanent deficits reduce quality of life and survival time
McGirt et al. Neurosurgery 2009



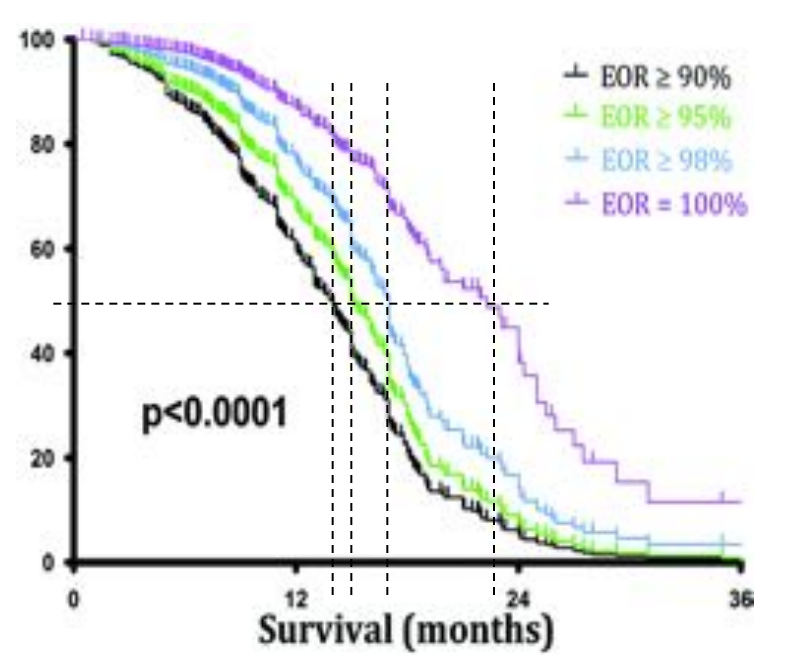


Glioma surgery: the oncology vs. neurology problem

Maximum resection ↔ No deficits

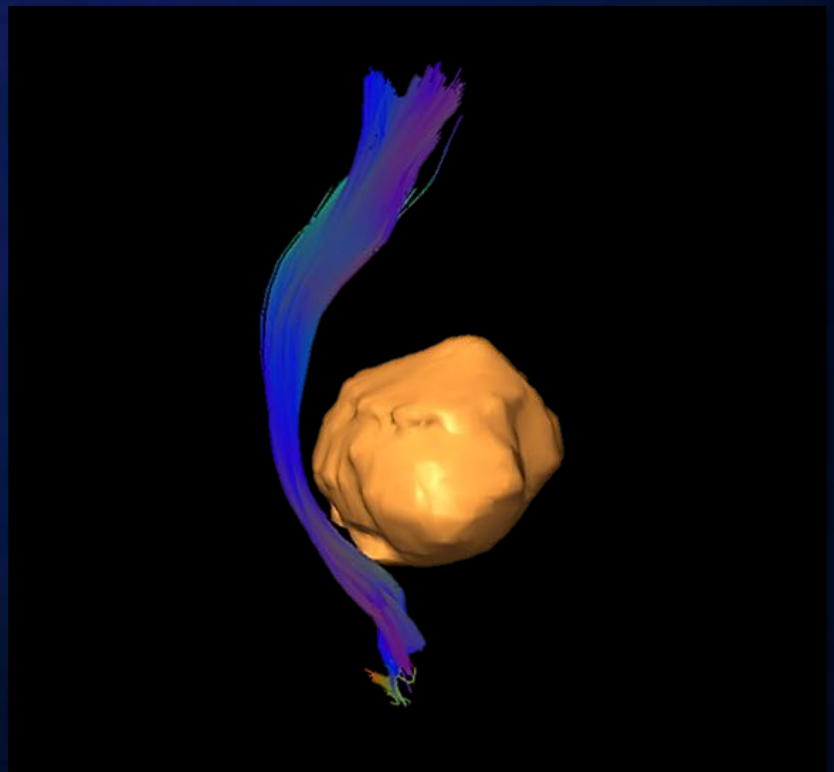
The final 1-2% may matter most in terms of overall survival.

The final 1-2% may be the most dangerous part of resection.



Glioblastomas

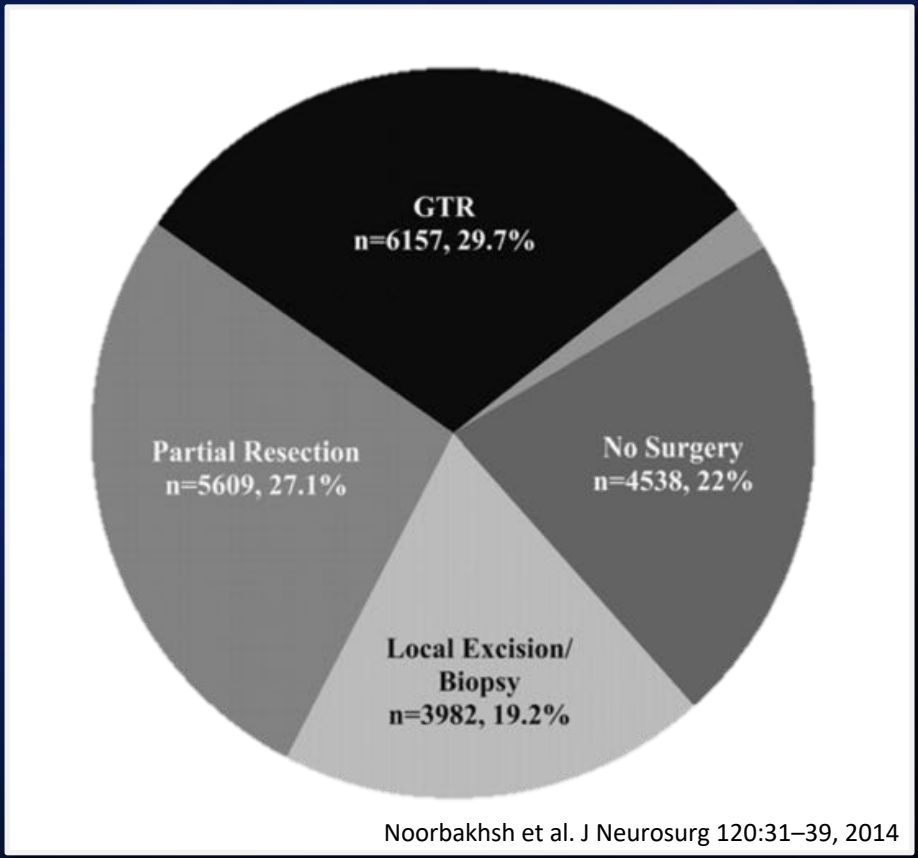
Sanai et al. J Neurosurg 115:3–8, 2011



Real world results of glioblastoma surgery

20705 adult patients with glioblastoma

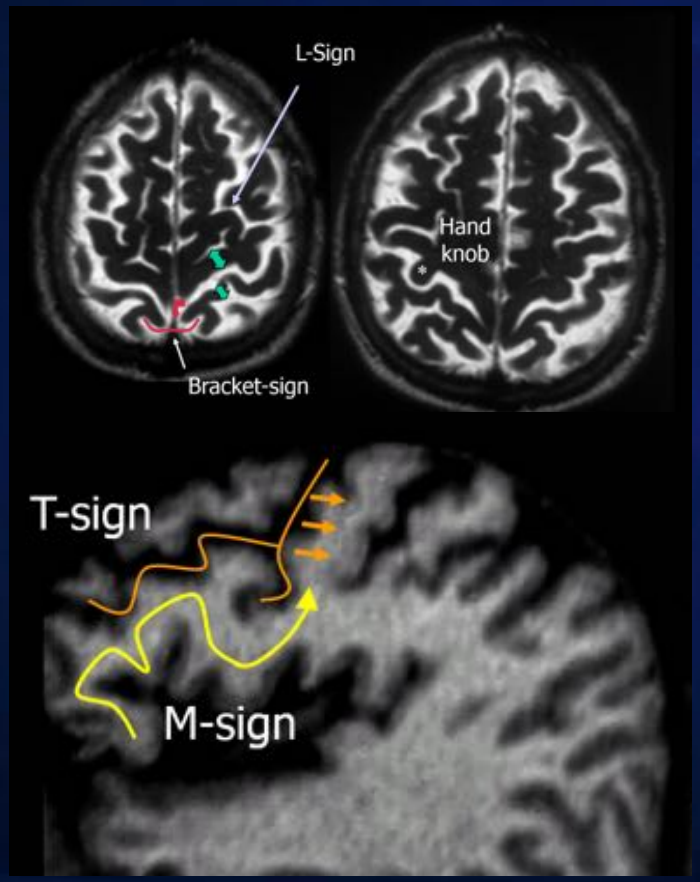
in the Surveillance, Epidemiology, and End Results (SEER) registry (1998–2009)



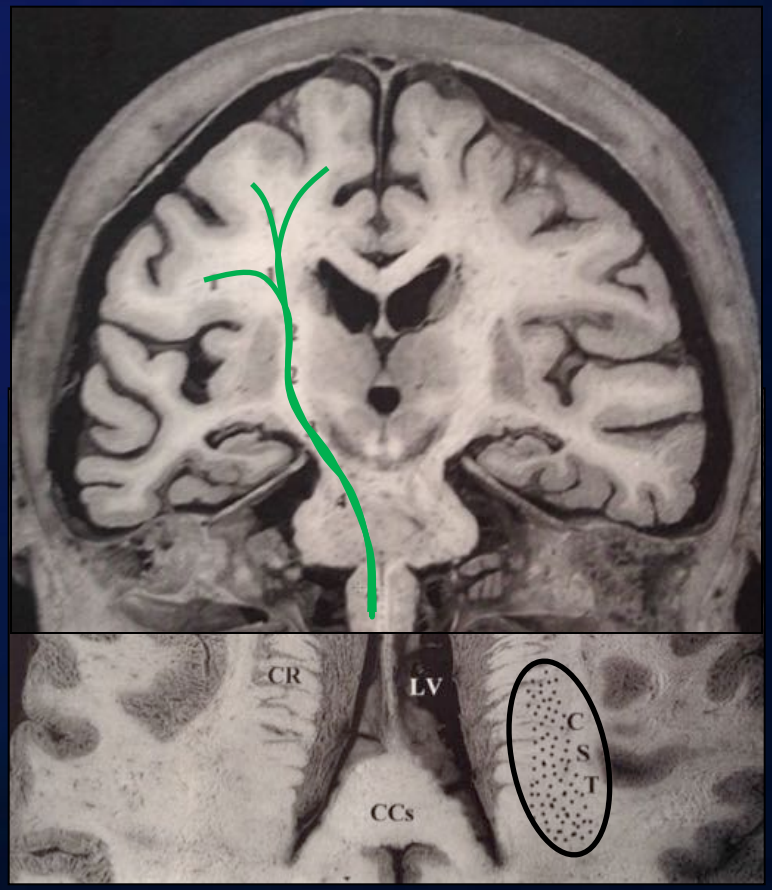
Noorbakhsh et al. J Neurosurg 120:31–39, 2014

Identify presumed motor eloquence

Cortical



Subcortical

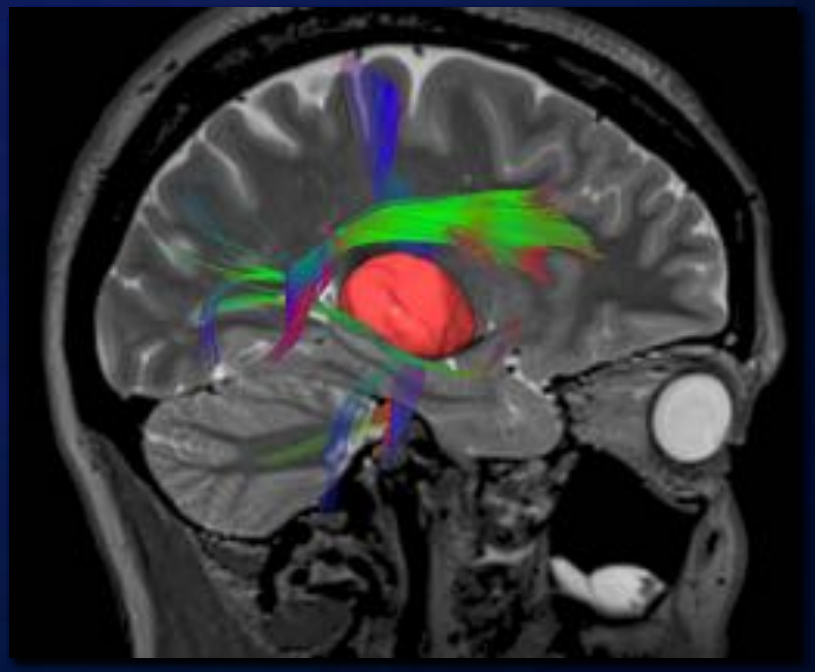


Fibertracking (fMRI, TMS) and approach planning

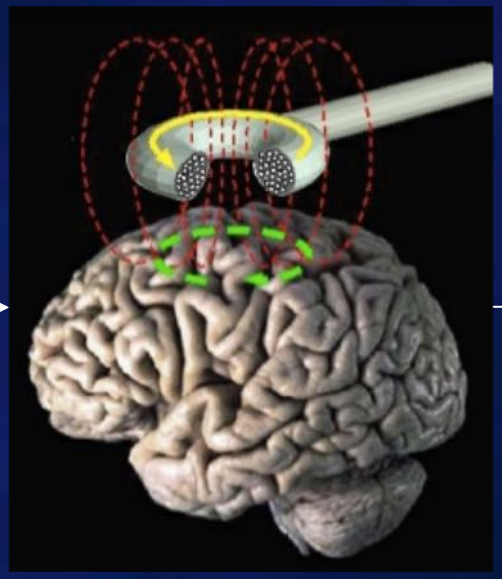
Diffusion tensor imaging and fiber tracking
- corticospinal tract
- optic tract
- arcuate fascicle

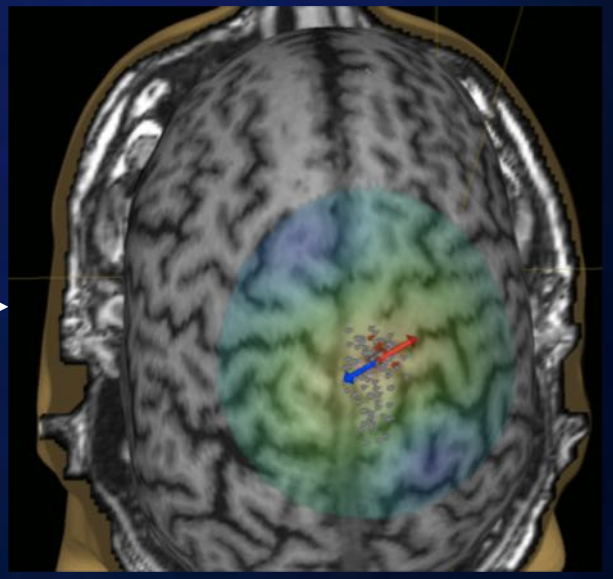
Navigation planning
- anatomy synthesis

Planning of craniotomy, approach and electrophysiology



Navigated repetitive transcranial magnetic stimulation

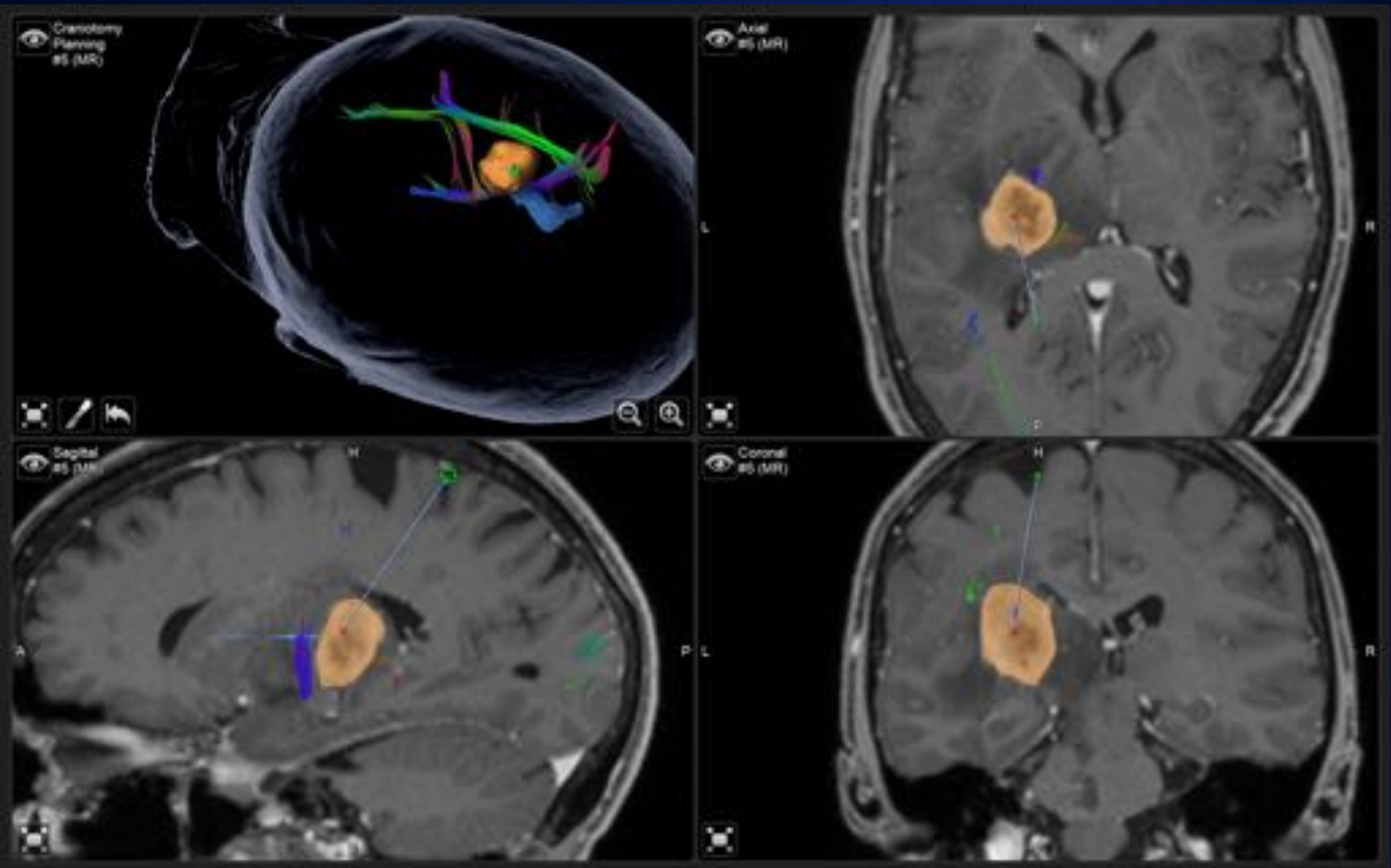




\+ localizing motor cortex in 3D space
can be navigated

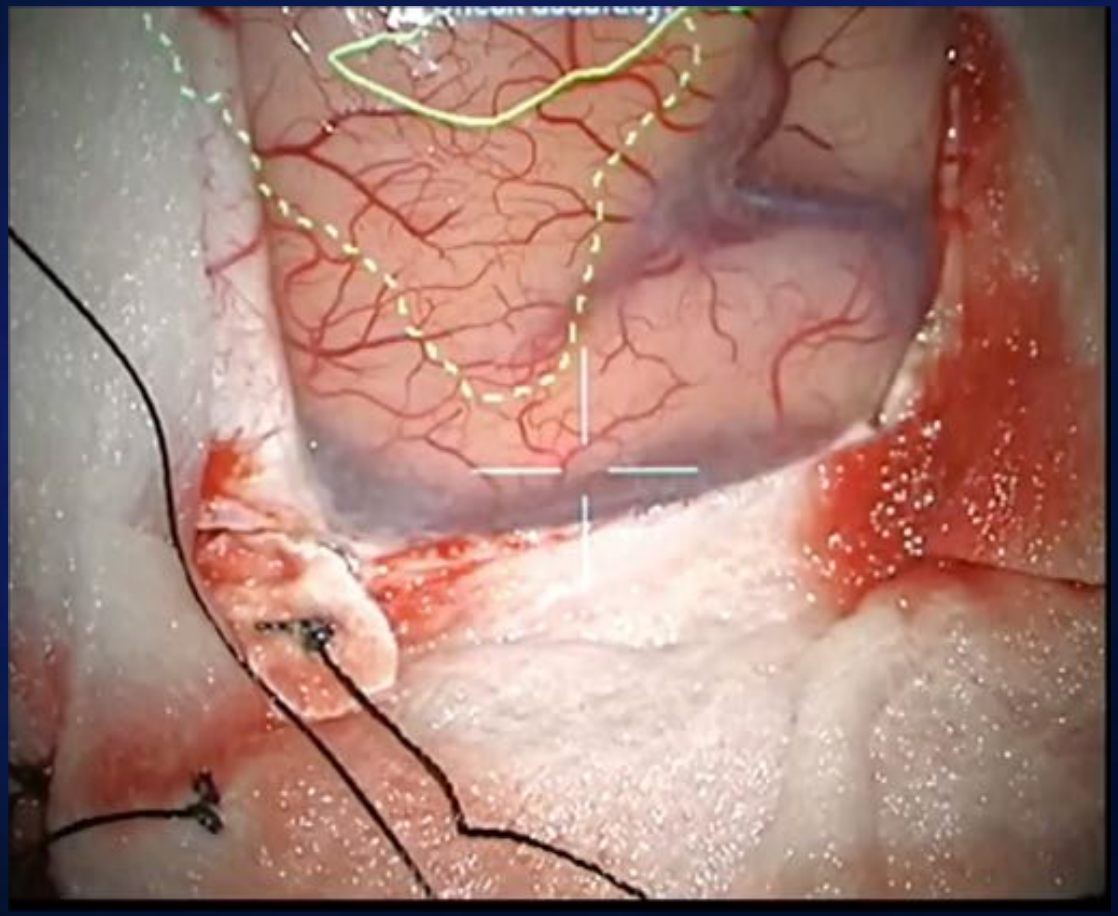
? additive value to mapping?
clinical consequences?

Planning of craniotomy, approach and electrophysiology



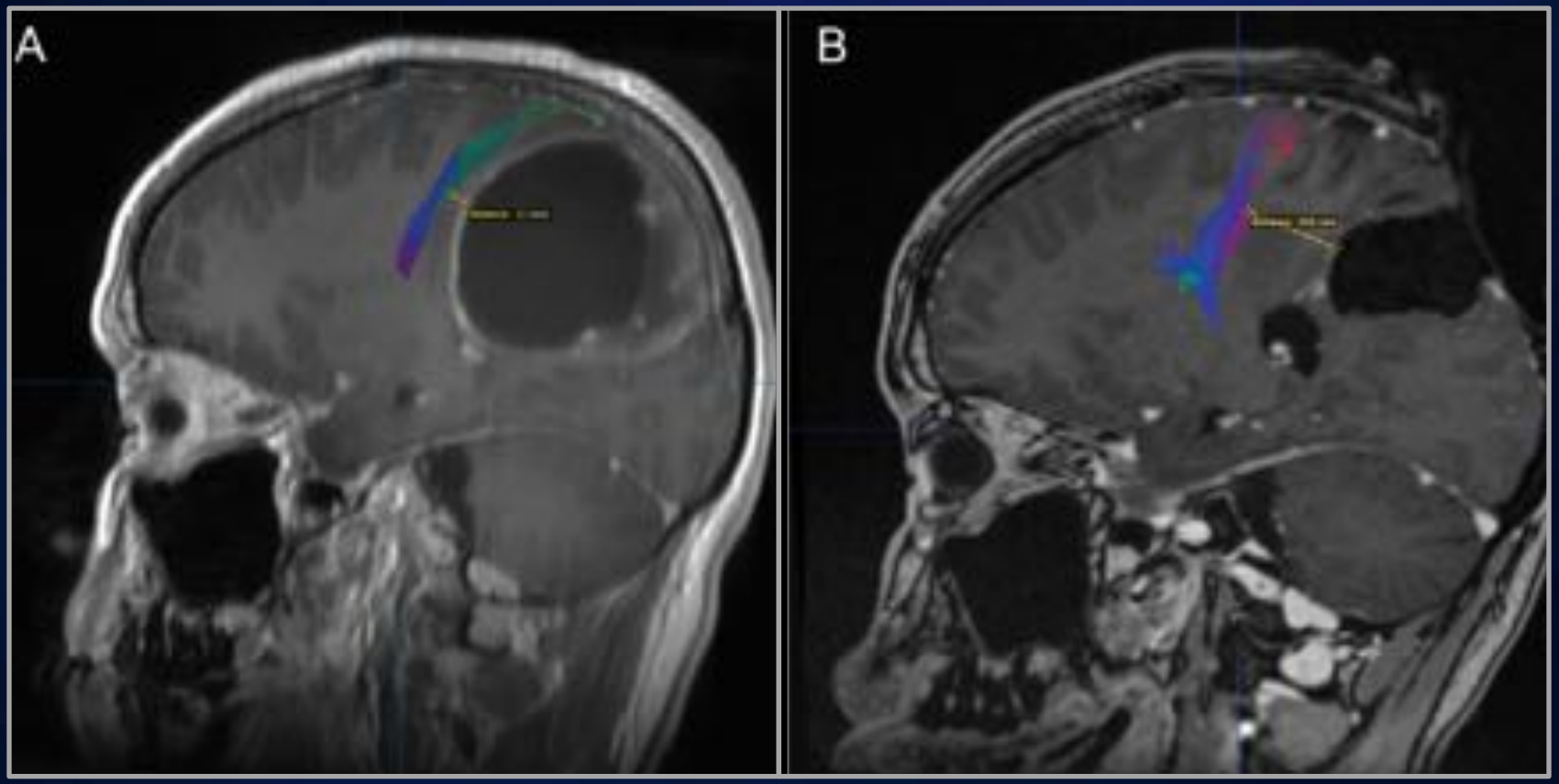
Avoidance of vascular injury: going subpial

Identification of sulcal borders (deep sulcal extension of the tumor) → Cortical parasulcal incision → subpial tumor stripping with preservation of pial arteries



Imaging is unreliable to protect function

Brain shift attributable to tissue elasticity: 0 – 19 mm



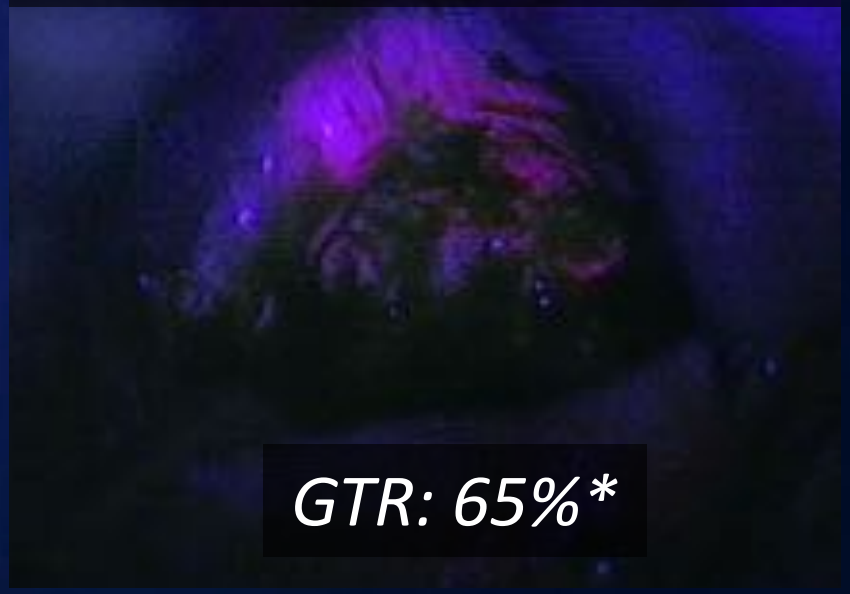
Sahar et al. Neurosurgery 2014

5-ALA fluorescence guided resection of malignant glioma: a multicenter phase III RCT

Stummer et al. Lancet Oncol 7:392-401, 2006

White light (n=139)

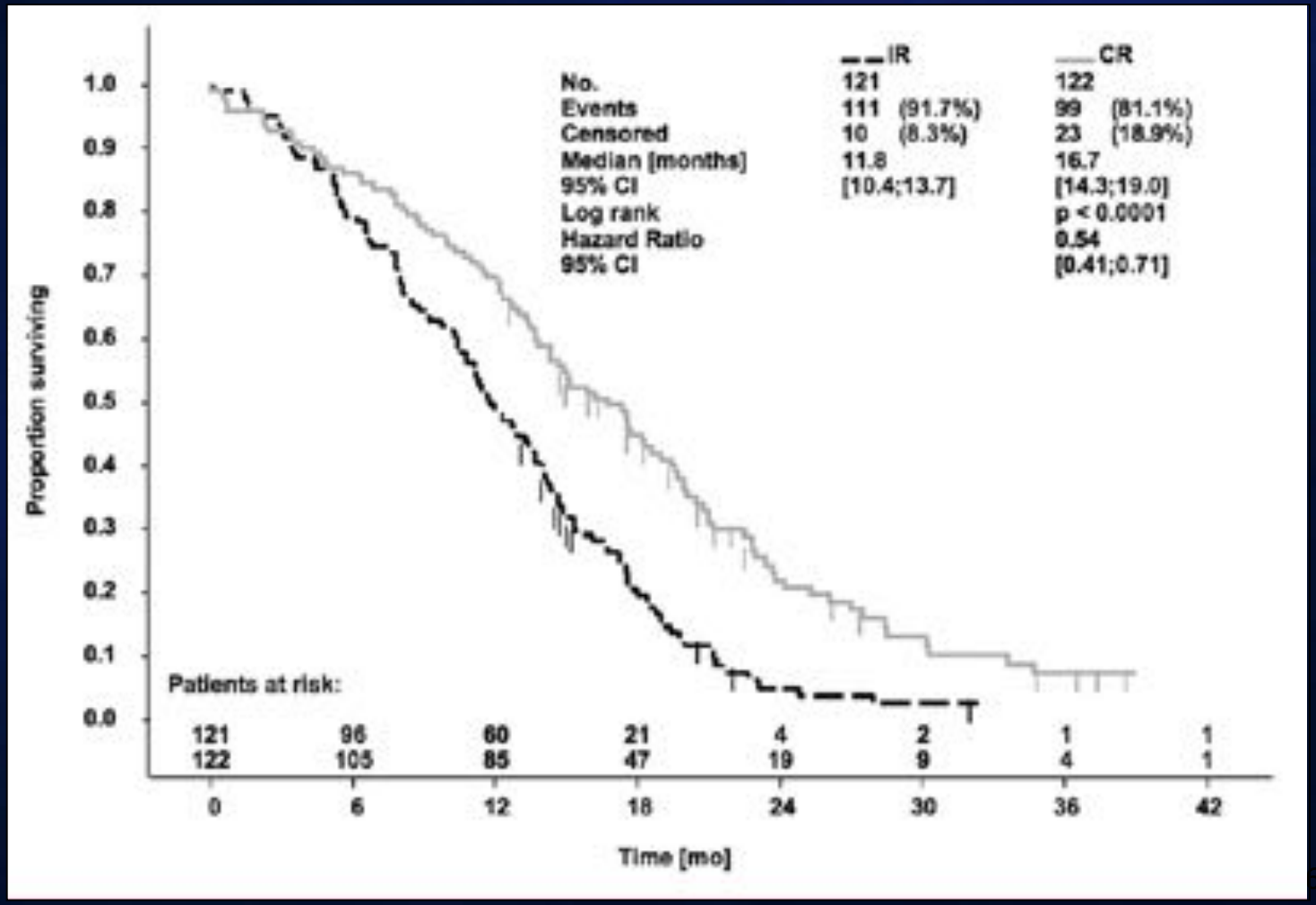
Blue 400 fluorescence light (n=131)



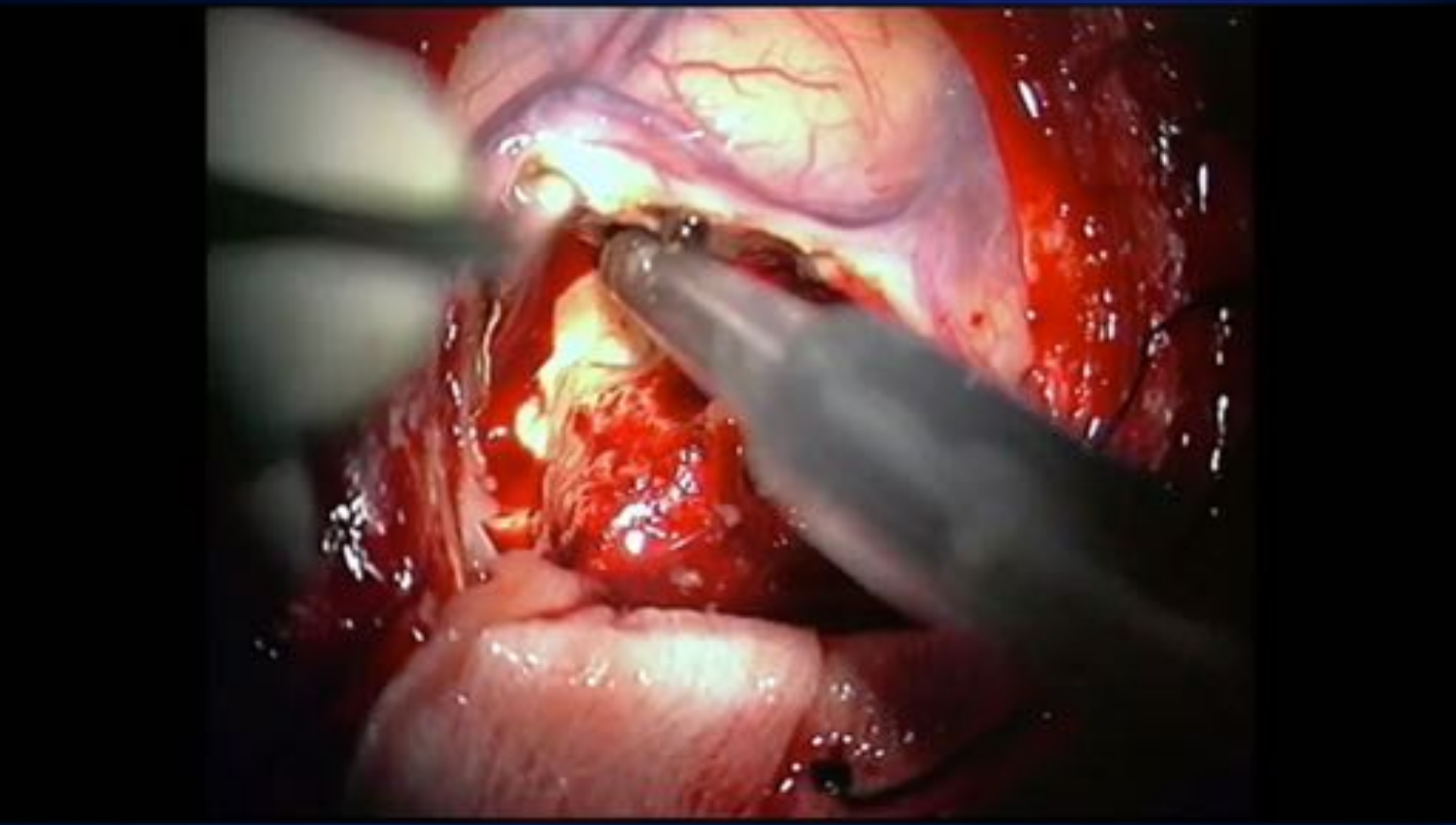
* $p < 0.0001$

Overall survival stratified by results of resection.

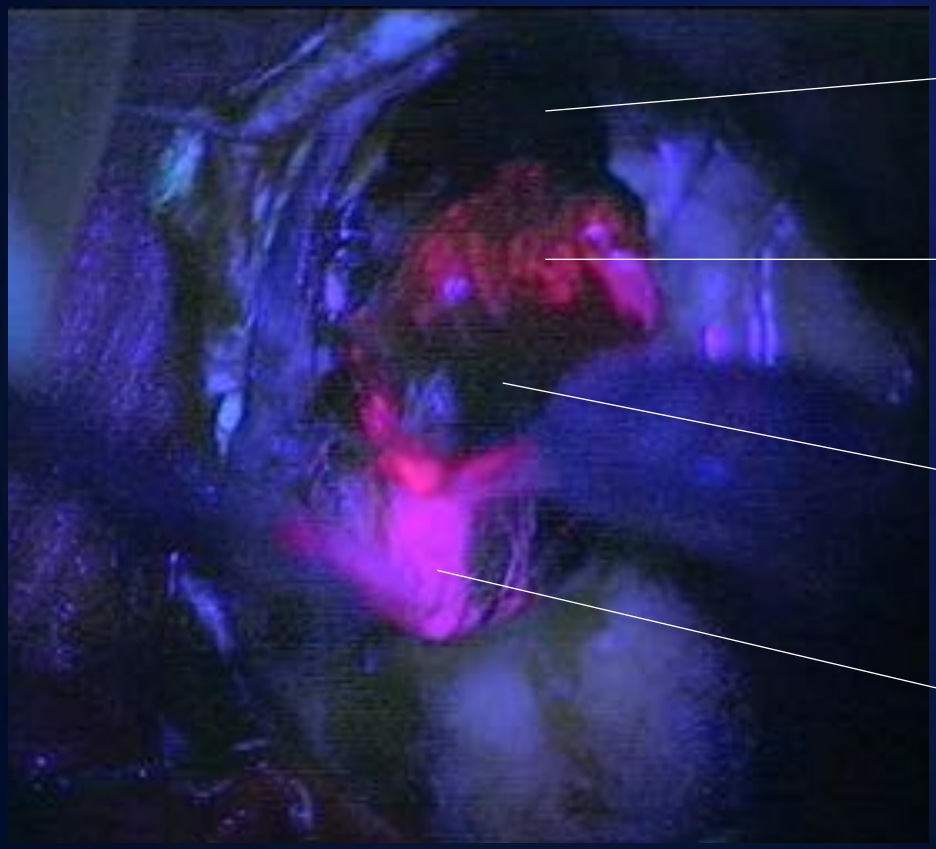
CR: complete resection, IR: incomplete resection



64-576, 2008



Fluorescence and tissue components of 5-ALA stained glioblastoma



no fluorescence
„normal tissue“
(NPV 40%, 0-25% infiltrating cells)

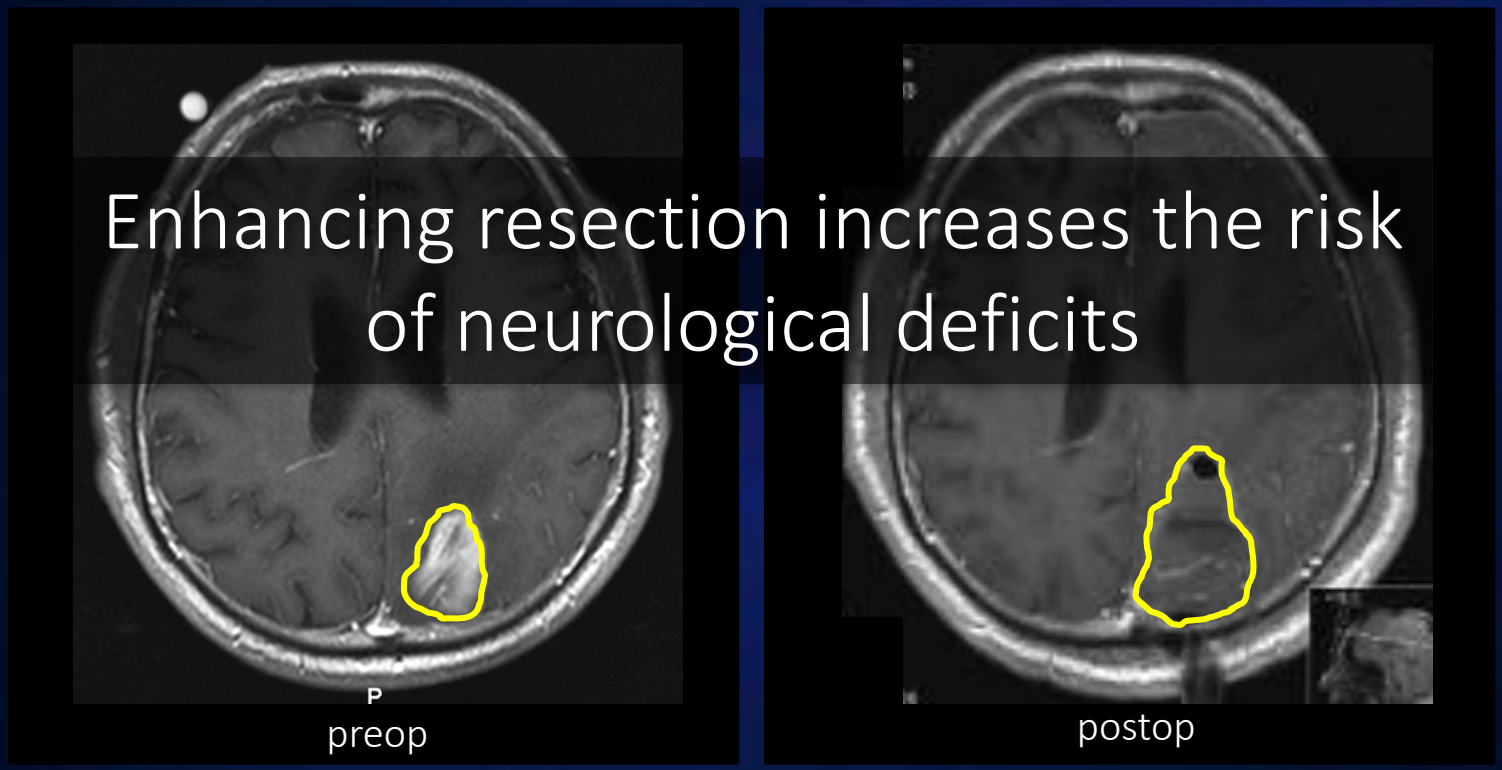
solid pink fluorescence
tumor bulk, completely shown in Gd+ MRI
(PPV 100%, 60-90% infiltrating tumor cells)

no fluorescence inside solid pink fl.
necrosis in Gd+ MRI
necrosis and tumor cells

faint or vague fluorescence
infiltrative tumor only partially shown in Gd+ MRI
(PPV 92%, 10-60% infiltrating tumor cells)

Stummer et al. Neurosurgery 2013

5-ALA resections go beyond MRI tumor



preop

postop

Enhancing resection increases the risk of neurological deficits

5-ALA guided resected tumor volume on average 200% of MRI-T1 Gado+ volume

Schucht et al. Acta Neurochir. 2014

Challenge:
to protect quality of life and neurological function

Tools to avoid deficits

Electrophysiology

Awake surgery
50 Hz Mapping

- Language deficits
- Visual field deficits
- Higher function deficits

General anesthesia
250 Hz / short train

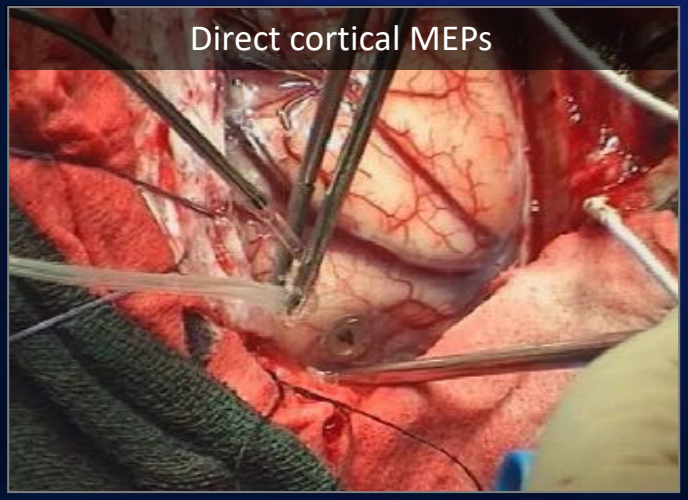
MEP-monitoring
Mapping

- Motor deficits

Bern approach:
MEP monitoring & continuous dynamic mapping

Transcranial MEPs

Direct cortical MEPs



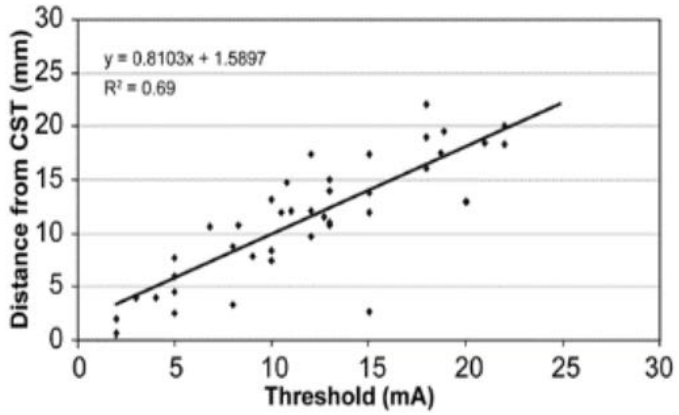
Continuous dynamic mapping (train of five, acustic feedback)

Continuous dynamic mapping
Distance radar

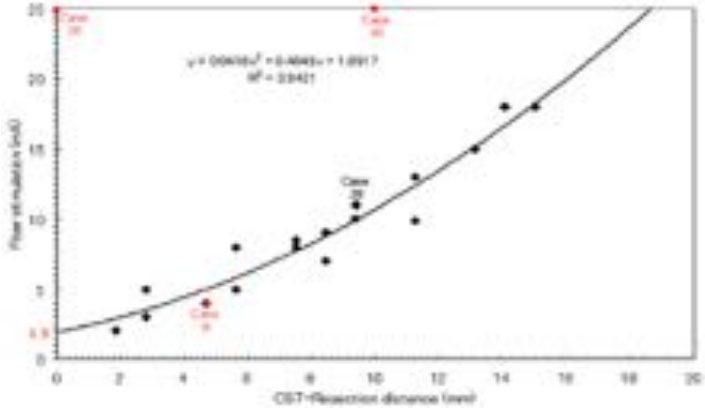
Monopolar cortical or subcortical mapping:
Stimulation intensity = Distance radar diameter

Raabe et al. J Neurosurg 120:1015–1024, 2014

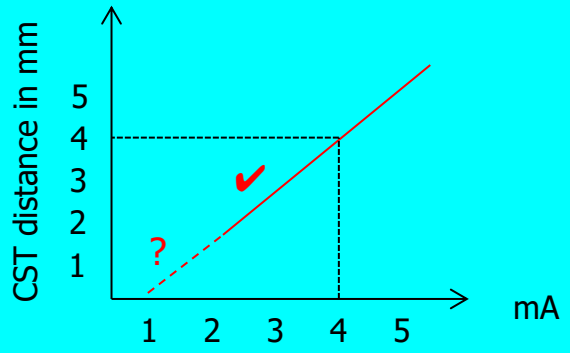
Distance to CST = Stimulation intensity for MEP



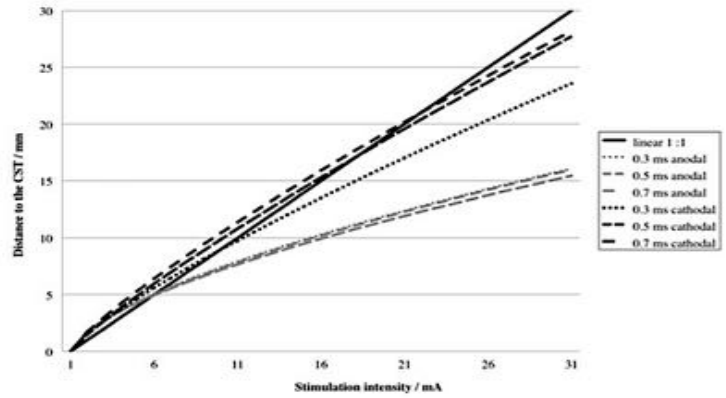
Distance = 0.8 * mA + 1.6 mm
Electrical threshold of the CST: 1.6 mA
Nossek et al. JNS 2011



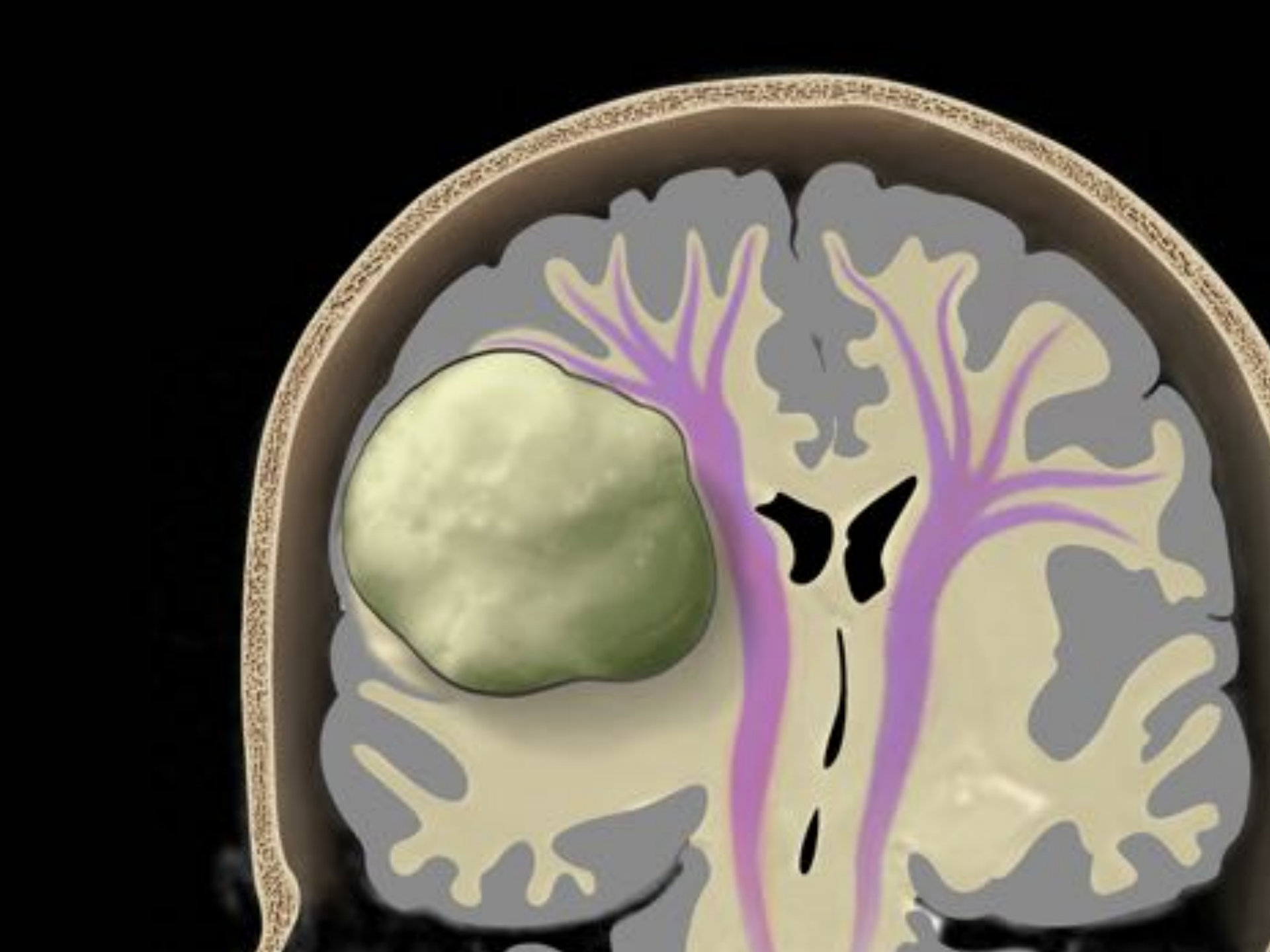
$y=0.0416\ x^2 + 0.4649\ x + 1.891$
Electrical threshold of the CST: 1.9 mA
Kamana et al. JNS 2009

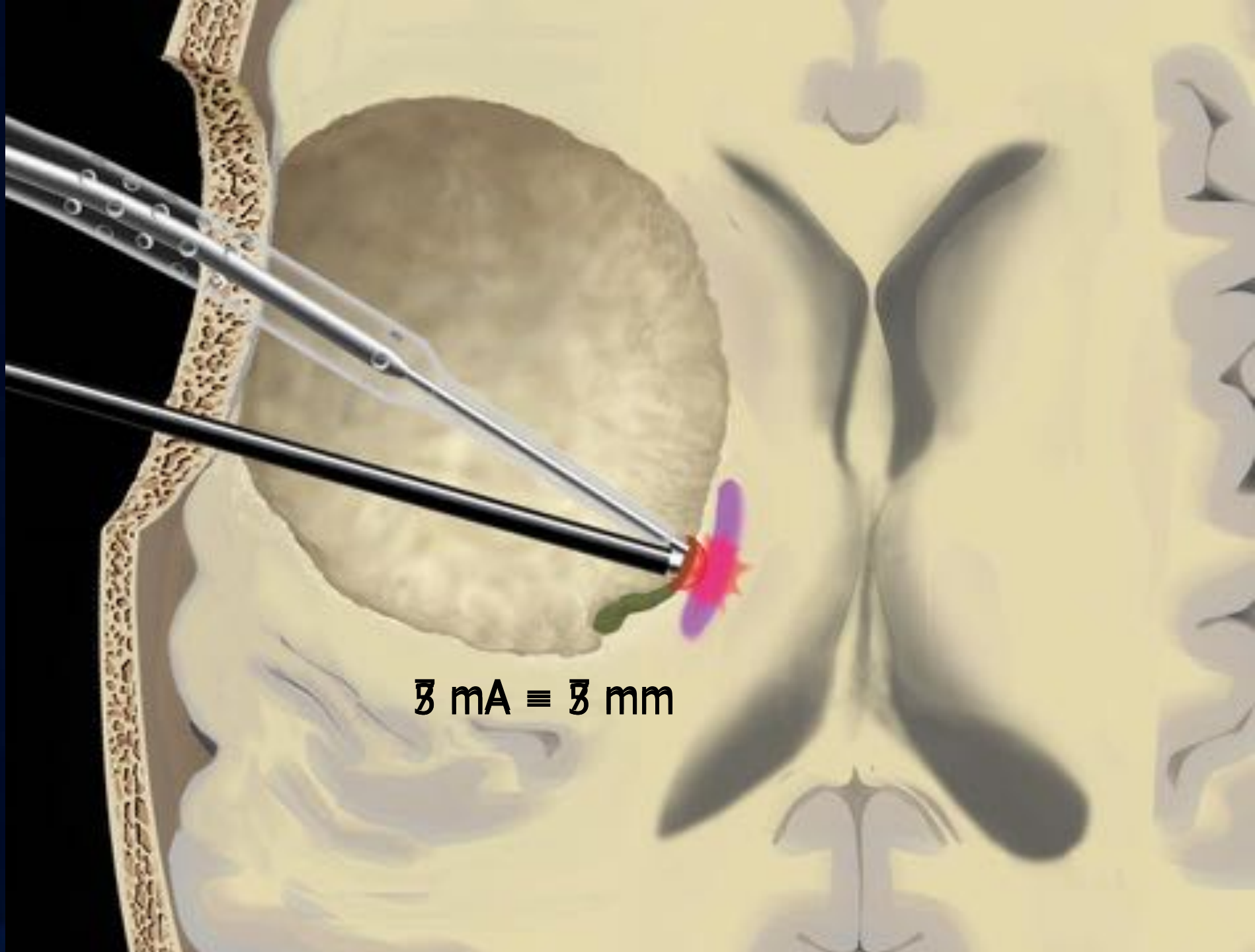


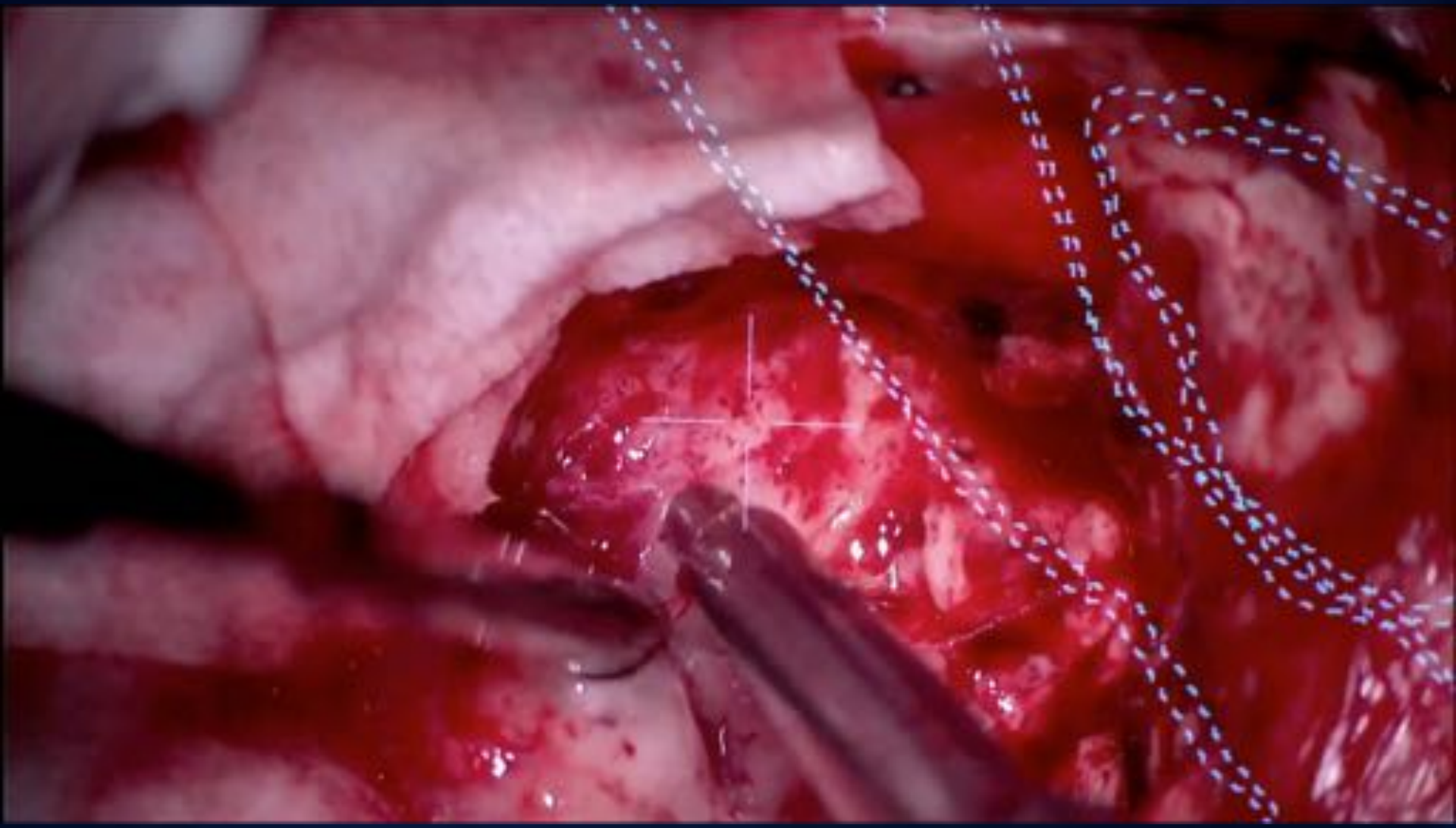
1mA = 1mm (at >2 mA)
Bern "Surgeons rule of thumb“
Electrical threasold of the CST <1mA
Seidel et al. Neurosurgery 2012



Distance = roughly 1 mm per 1 mA (cath.)
Electrical threshold of the CST: 1 mA
Shiban et al. JNS 2015




3 mA ≡ 3 mm



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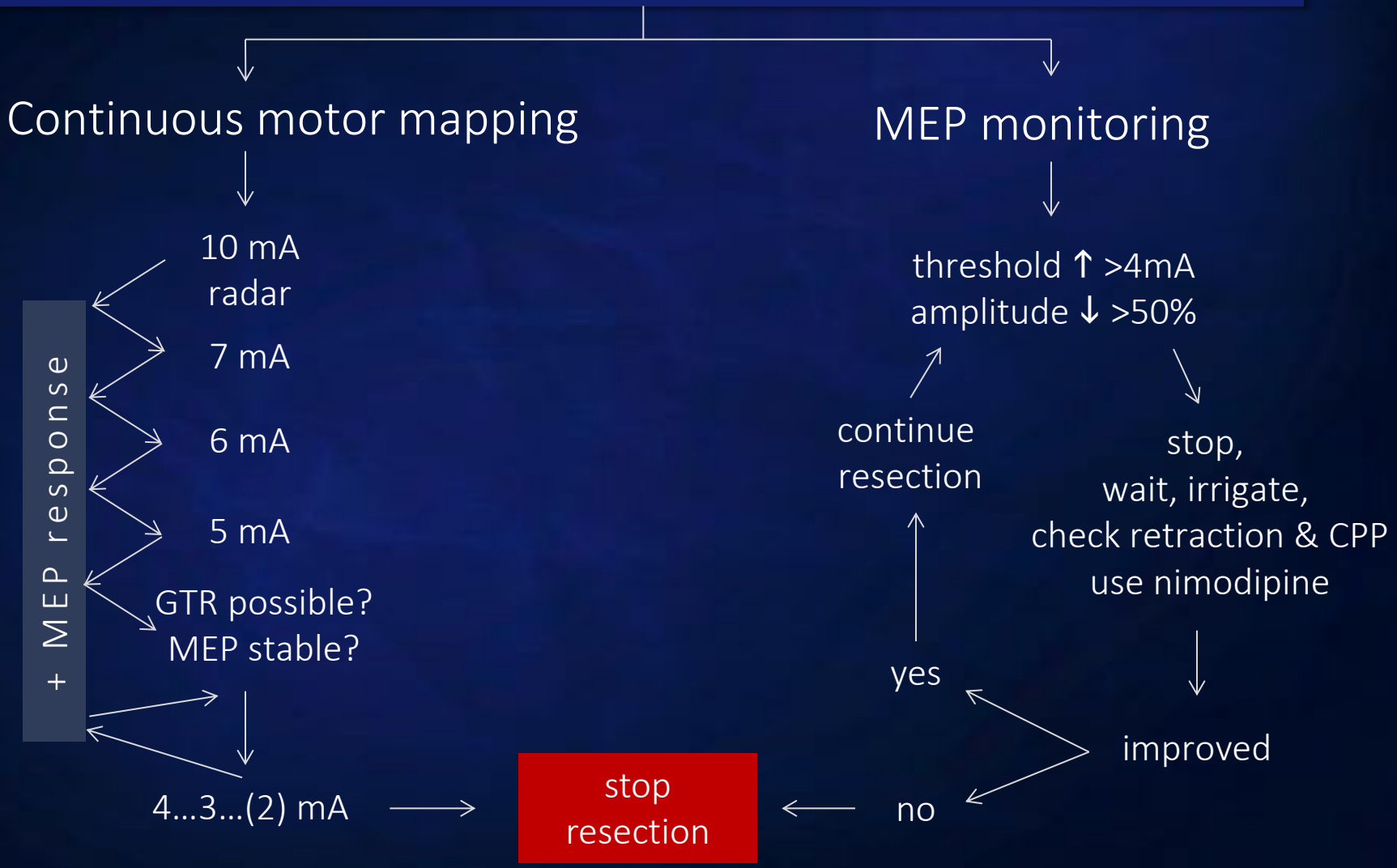
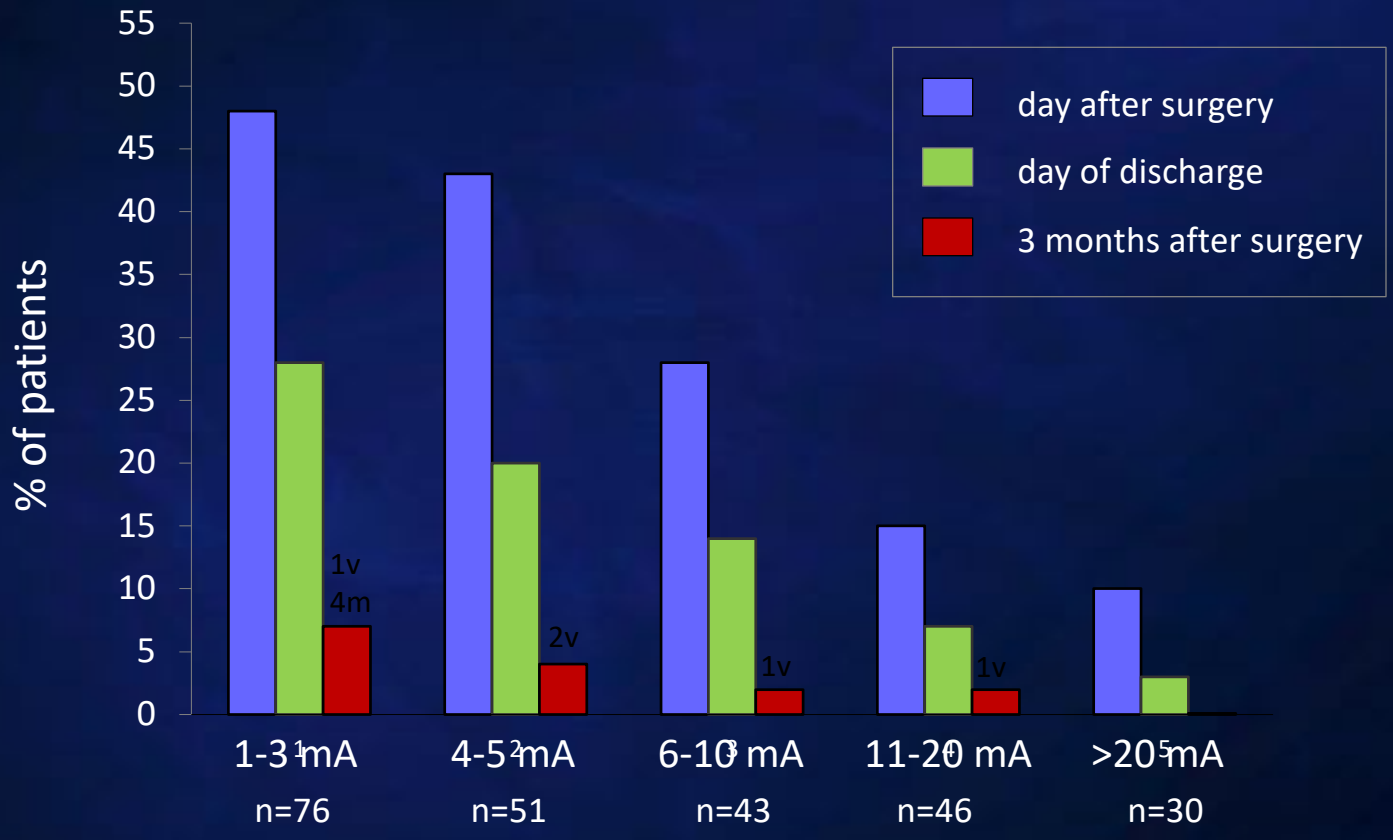
Bern concept for motor tumors



New motor deficits after surgery of motor eloquent brain tumors

246 patients: 9 patients (3.7%) permanent motor deficits

5 vascular, 4 mechanical injuries



Preservation of “higher” functions

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Mapping

- ✓ Bipolar, 50 Hz, patient awake, performs specific tasks
- ✓ Ice water irrigation, Keppra loading, ready for seizure control
- ✓ Cortical and subcortical mapping, making errors is the test

Preservation of “higher” functions

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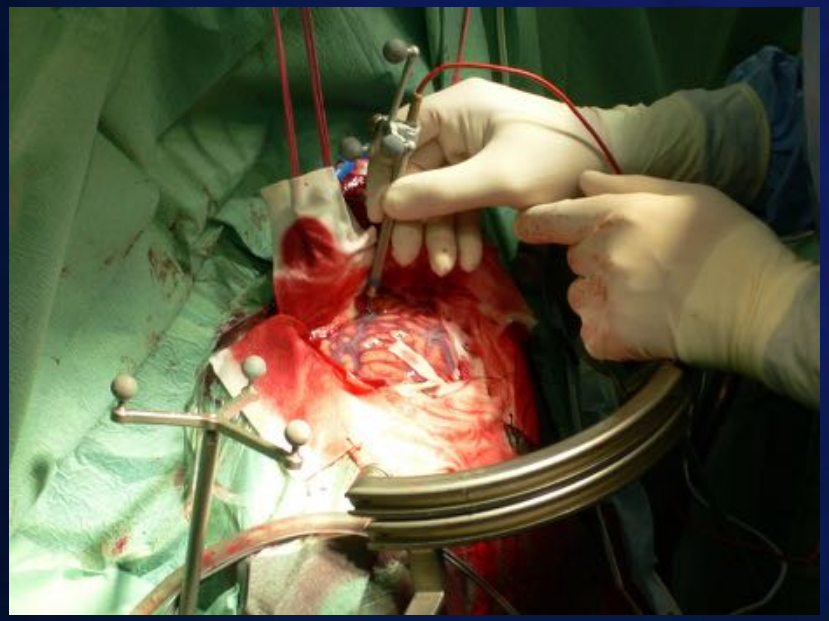
Mapping

- ✓ Error = positive mapping = no resection (no distance rule!)
- ✓ Area of 1 cm is regarded a safe distance
- ✓ Areas are marked to be preserved



Meta-analyzing left hemisphere language areas: Phonology, semantics, and sentence processing

M. Vigneau,[a,1] V. Beaucousin,[a,1] P.Y. Hervé,[a] H. Duffau,[c] F. Crivello,[a] O. Houdé,[a] B. Mazoyer,[a,b] and N. Tzourio-Mazoyer[a,*]

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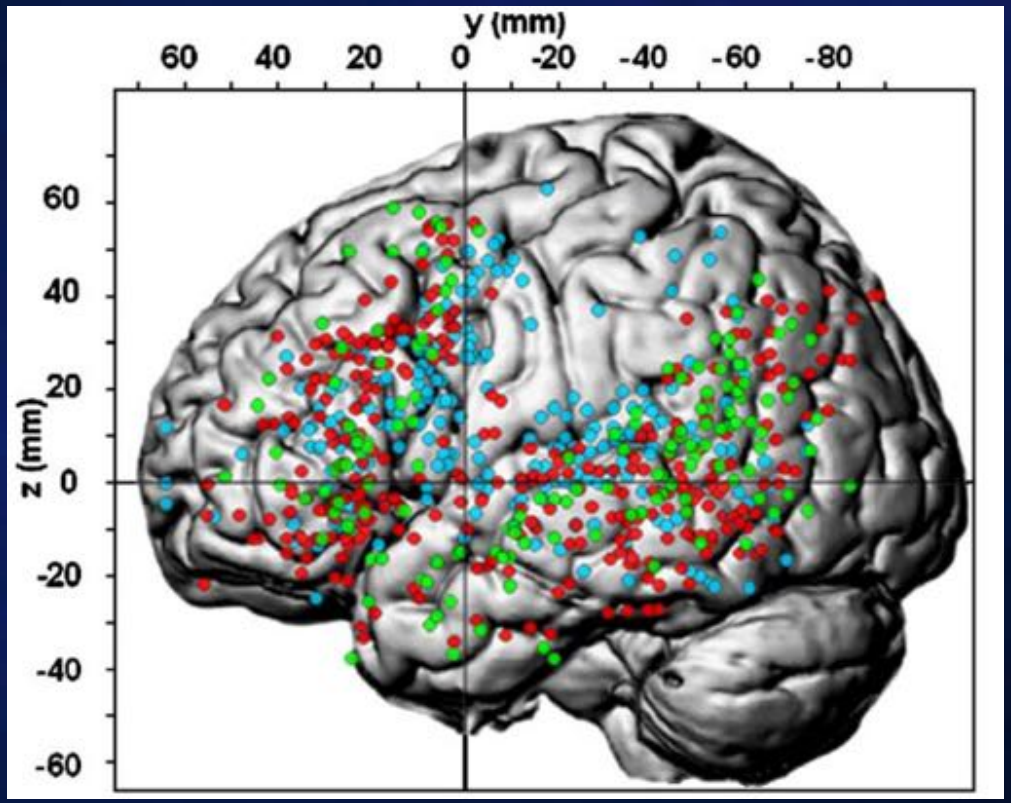
[b]*MR Unit Caen University Hospital, and Institut Universitaire de France, France*
[c]*Department of Neurosurgery, Hôpital La Salpétrière, France*



NeuroImage
www.elsevier.com/locate/ynimg
NeuroImage 30 (2006) 1414 – 1432

73 y, female

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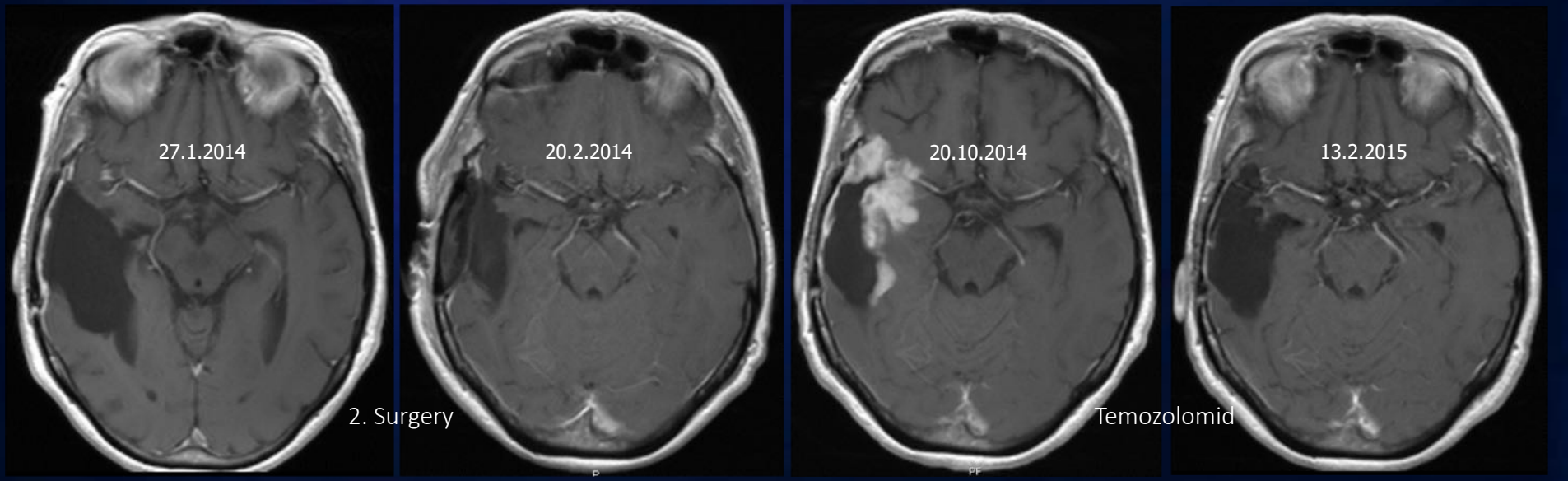
Surgery

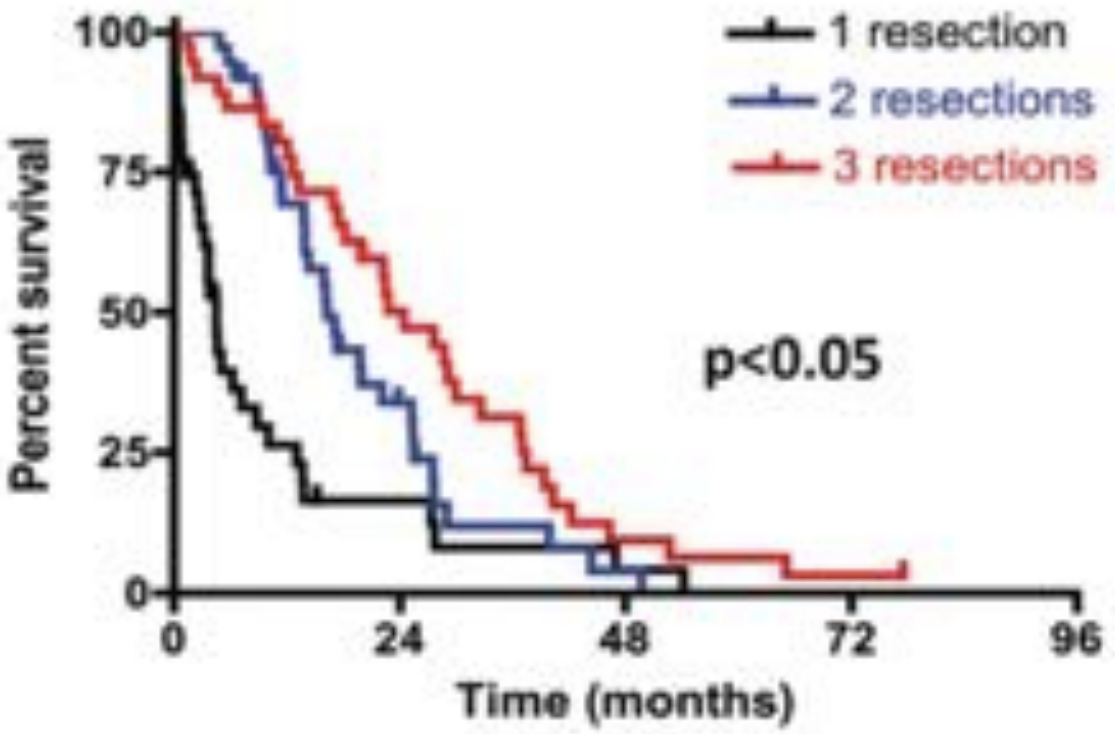
Radiotherapy (MGMT meth. negative)



2. Surgery

Temozolomid

Surgery for recurrent glioblastoma and survival: pro

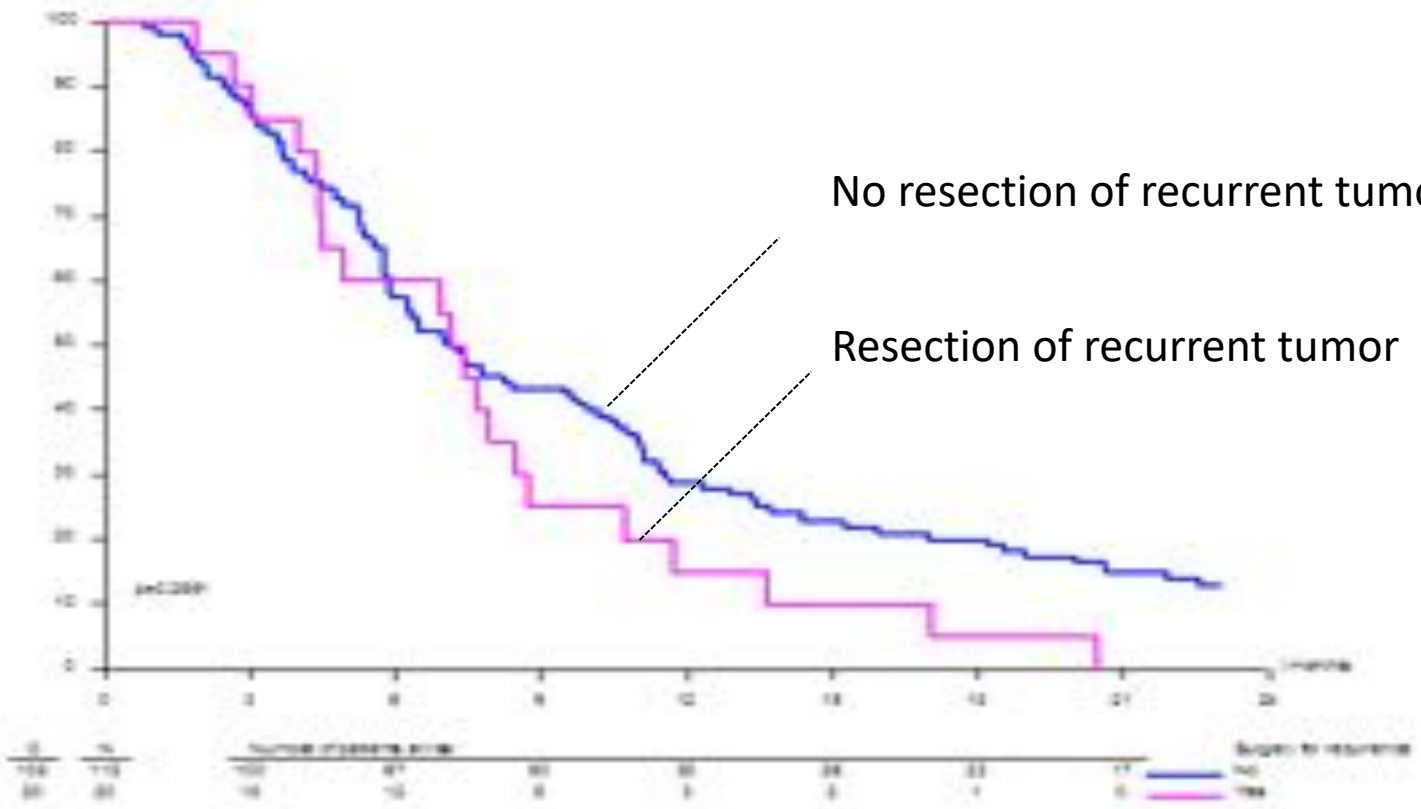


4.5 (?)
16.2
24.4 months

Kaplan-Meier curves for patients who underwent 1, 2, or 3 resections from the time of initial glioblastoma diagnosis. Groups were matched for age, preoperative KPS score, periventricular tumor location, extent of resection, and temozolomide/radiation therapy. The median survival was 4.5, 16.2, and 24.4 months for patients who underwent 1, 2, or 3 resections, respectively. Patients who underwent 1 resection experienced significantly shorter survival than patients with 2 ($p = 0.002$) or 3 ($p = 0.0001$) resections. Patients who underwent 2 resections had significantly shorter survival times than patients with 3 resections ($p = 0.05$).

Chaichana et al. JNS 118:812-820, 2013

Surgery for recurrent glioblastoma and survival: con



Gorlia et al. Eur J Cancer 48(8):1176-84, 2012

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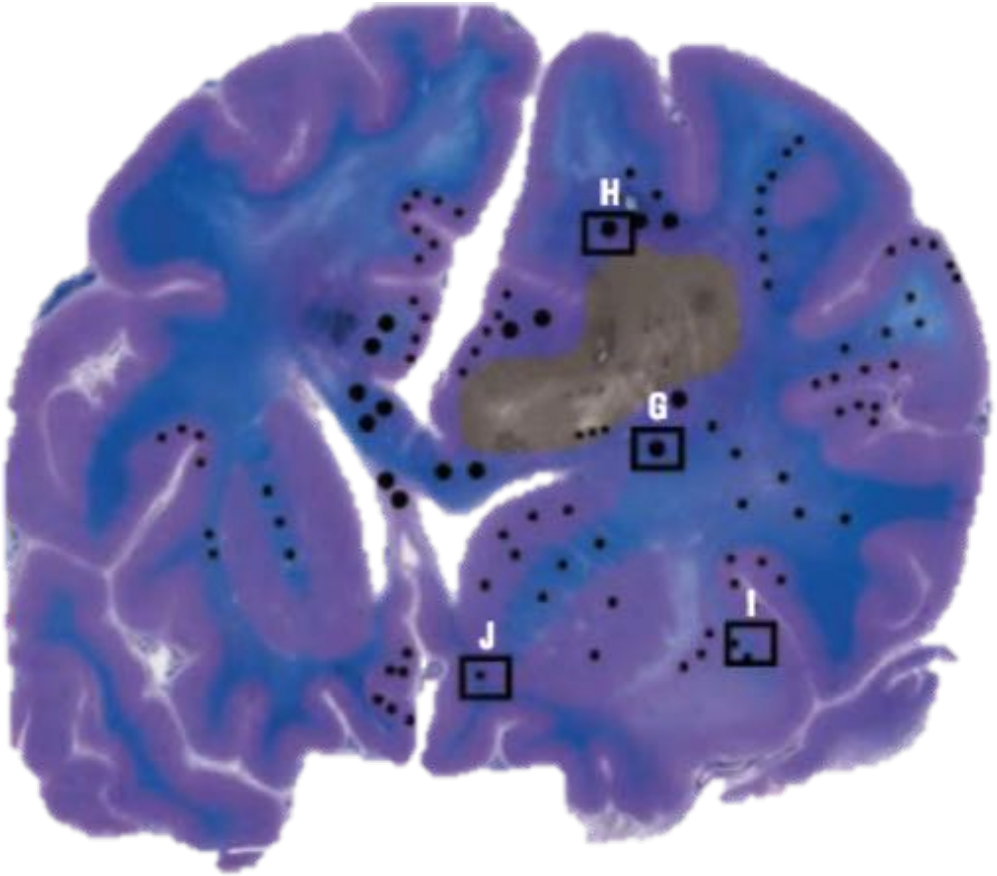
reSurge

To assess survival and functional outcome after surgery followed by adjuvant second-line therapy versus second-line therapy in recurrent glioblastoma in a randomized multicenter trial.

Study investigators: Schucht, Weller, Stupp, Beck, Ochsenbein, Regli, Raabe and the Swiss Glioma Network

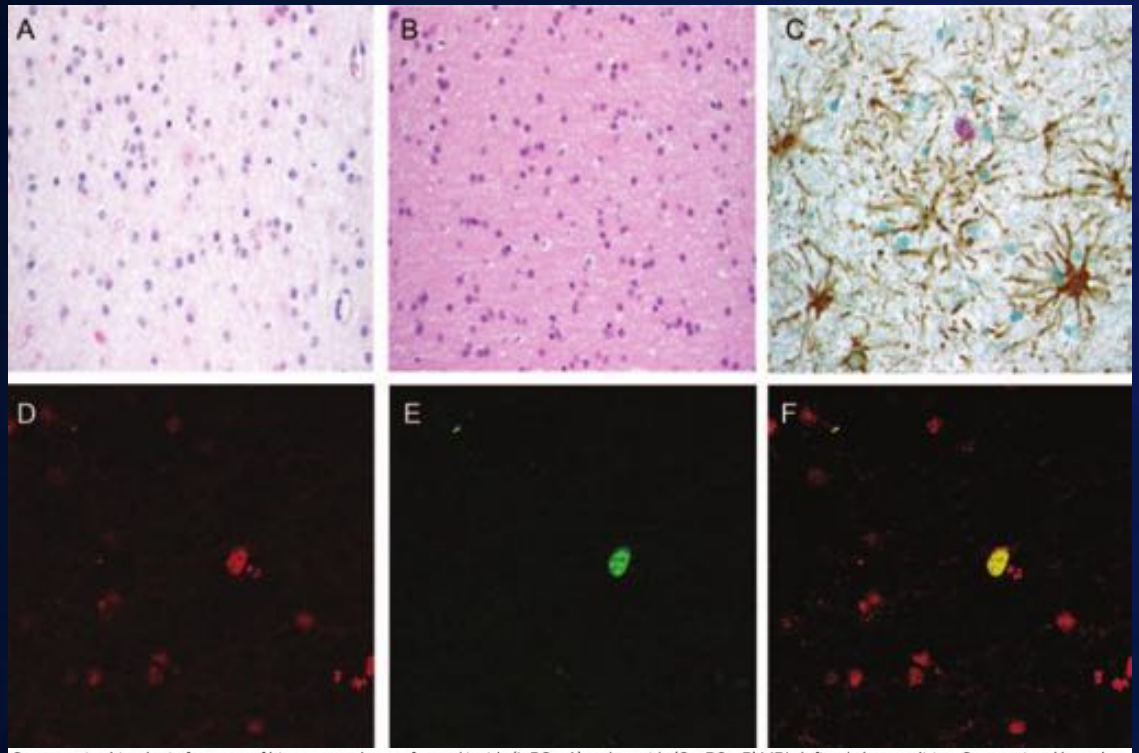
Challenge:
to develop new treatments for non-resectable gliomas

Glioma – a systemic brain disease



Sahm et al. Arch Neurol 2012:69(4):523-526

Diffuse LGG extend beyond MRI boundaries



Comparative histologic features of biopsy samples performed inside (InBSs; A) and outside (OutBSs; B) MRI-defined abnormalities. Conventional hemalun-phloxin stainings showed that InBSs (A) are constituted, in the white matter, of infiltrative tumor cells associated by interstitial edema and gliosis (×400). In OutBSs (B), the white matter cell density appeared normal without any edema or gliosis (×400). Double immunostainings revealing that cycling cells do not shared astrocytic marker but correspond to Olig2-positive cells (C–F). Double chromogenic immunostaining revealed that Mib-1–positive cells (red) (i.e., cycling cells) do not share glial fibrillary acidic protein astrocytic marker (brown; C; ×600). Double immunofluorescent labeling showed that all Mib-1–positive cells (green; E) coexpressed the oligodendrocyte cell marker Olig2 (red; D) as observed on the overlay (F). Scale bar = 20 μm.

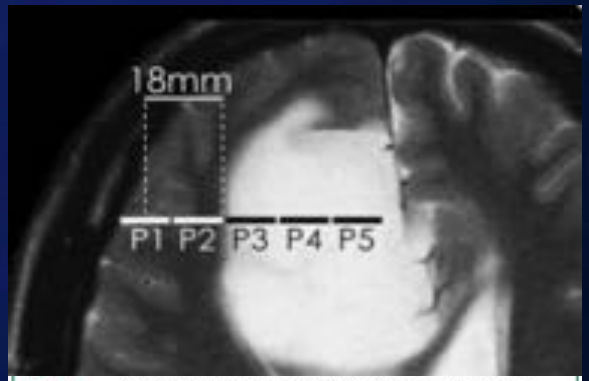
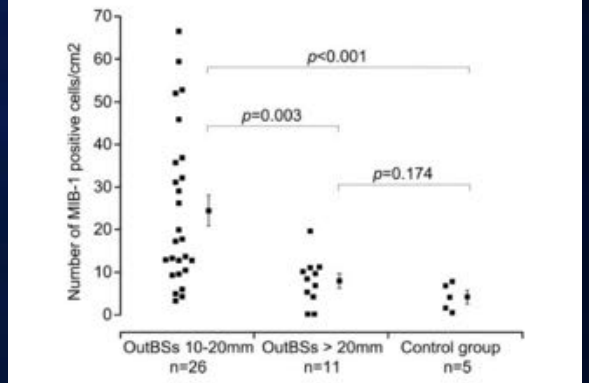


Figure 3 Significant decreasing gradient of the number of MIB-1–positive cells with the distance from the MRI-defined abnormalities

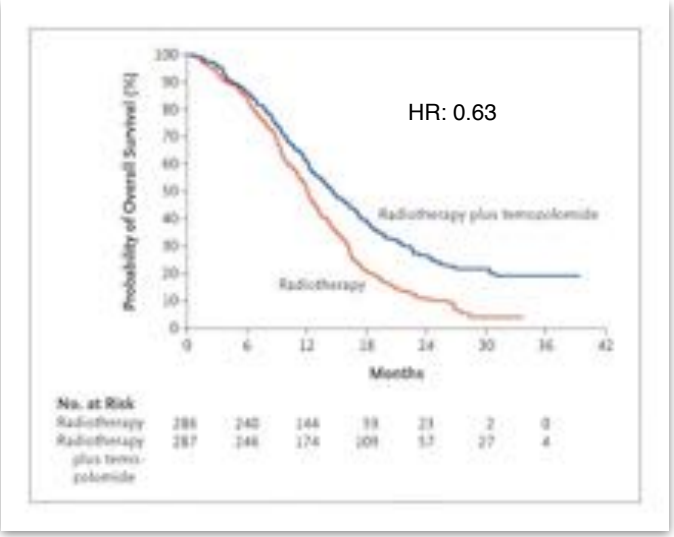


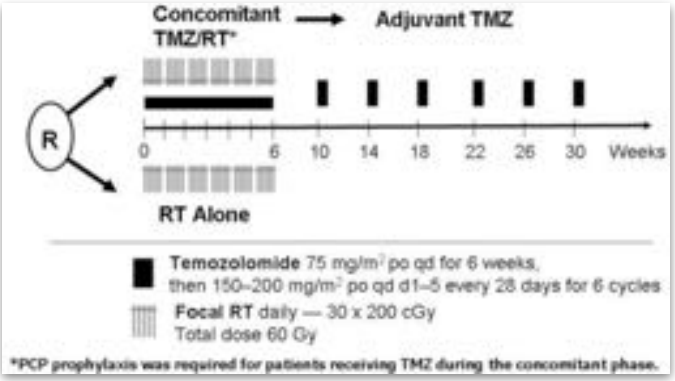
The number of cycling cells is expressed as MIB-1–positive cells per square centimeter, and the distance from MRI-defined abnormalities is expressed in millimeters. OutBS = biopsy sample taken outside MRI-defined abnormalities.

Pallud et al. Neurology 2010

Glioblastma

Treatment





Stupp et al. N Engl J Med 2005; 352:987-996

Glioblastma

MGMT - O-6-**m**ethyl**g**uanine-DNA **m**ethyl**t**ransferase

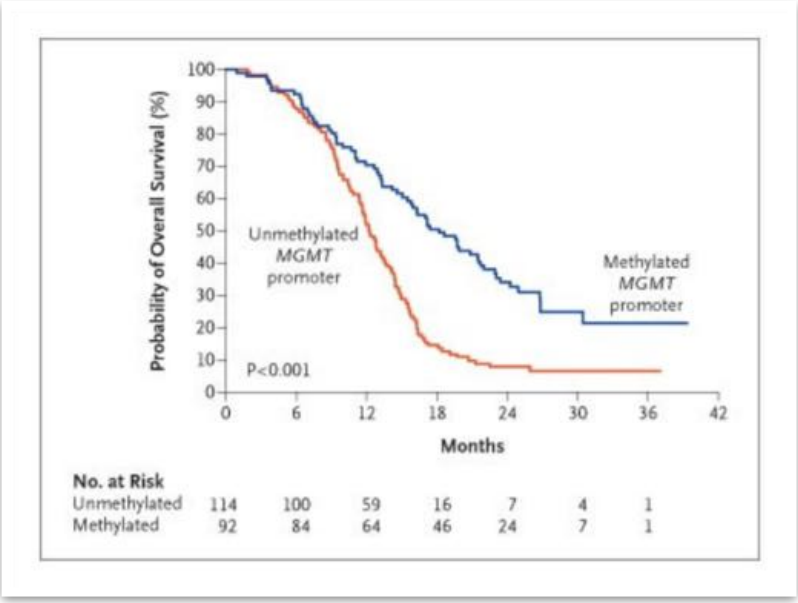
ORIGINAL ARTICLE

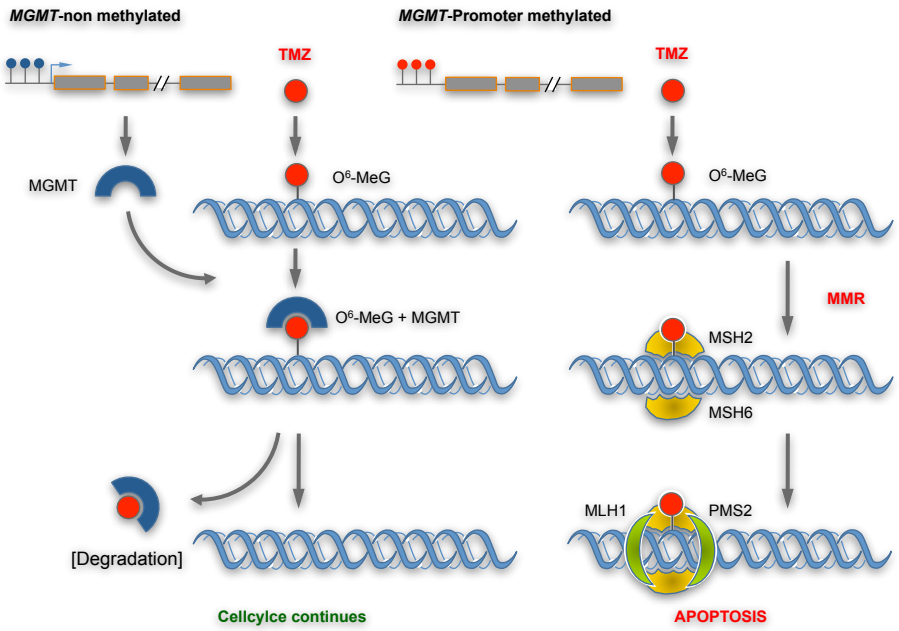
MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

N Engl J Med 2005; 352:997-1003 | March 10, 2005 | DOI: 10.1056/NEJMoa043331

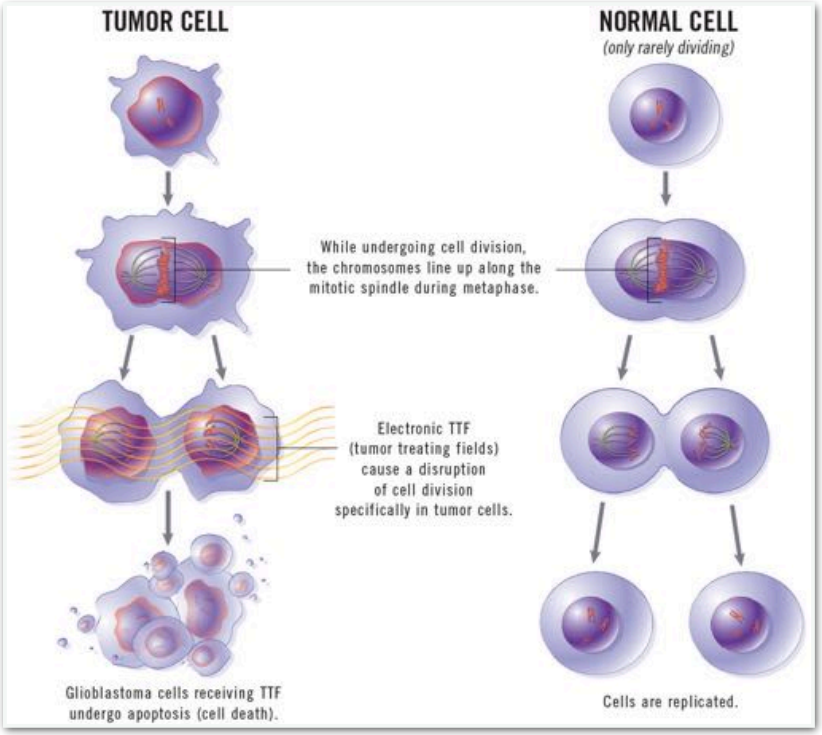
O-6-methylguanine-DNA methyltransferase
MGMT, a DNA repair enzyme. Methylation is described to impair DNA transcription and therefore, expression of the MGMT enzyme





Hegi et al., N Engl J Med 2005; 352:997-1003

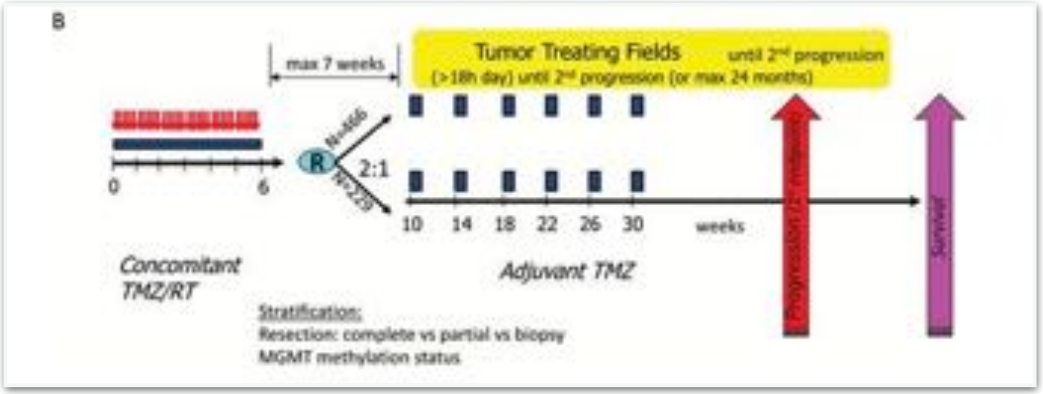
Tumor Treating Fields



Tumor Treating Fields, or TTFields, are low intensity, alternating electric fields (200kHz) that disrupt cell division through physical interactions with key molecules during mitosis in solid tumor cancers.

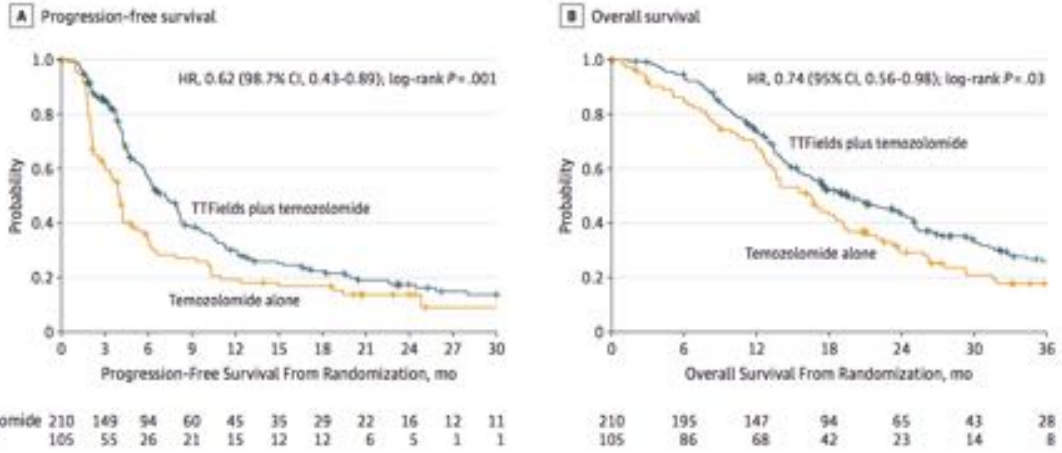
https://www.curetoday.com/publications/cure/2016/winter-2016/comments-from-readers-winter-2016

Tumor Treating Fields



Trial	Treatment arm	Number of patients	Progression-free survival		Overall survival	
			Median	at 6 months	Median	at 1 year
EF-14: newly diagnosed [Interim data set]	TTFields & TMZ	210 (466 total)	7.1 mo*	57%	19.6 mo	75%
	Maintenance TMZ	105 (229 total)	4.0 mo*	34%	16.6 mo	69%
	Hazard ratio		0.63 (CI, 0.43-0.89)		0.74 (CI, 0.56-0.98)	
	P value		< 0.01 (stat. significant)		0.0004 (stat significar	

Figure 2. Survival Curves for Patients Included in the Interim Analysis in the Intent-to-Treat Population



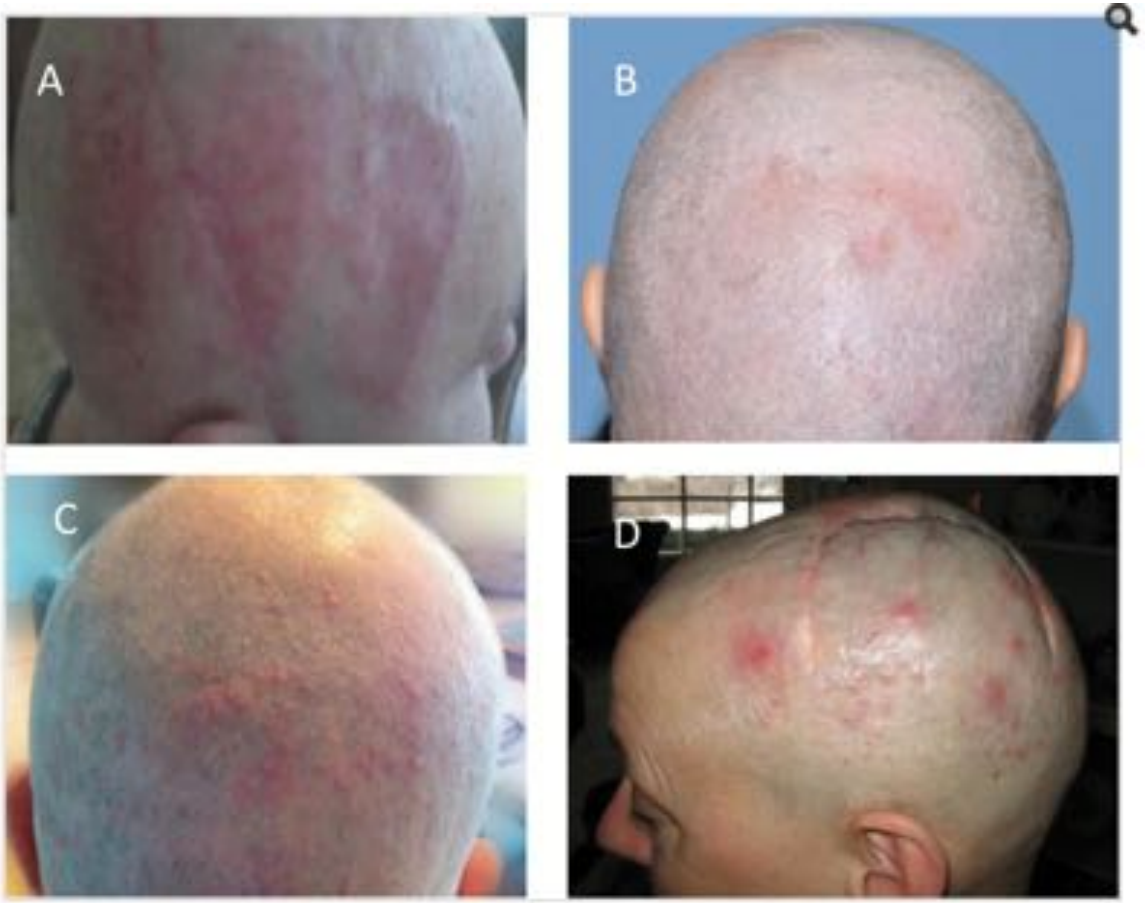
No. at risk

TTFields plus temozolomide	210	149	94	60	45	35	29	22	16	12	11	
Temozolomide alone	105	55	26	21	15	12	12	6	5	1	1	
	210	195	147	94	65	43	28					
	105	86	68	42	23	14	8					

Survival analyses on time from date of randomization until tumor progression, death, or last follow-up (censored patients) according to the Kaplan-Meier method. The small vertical ticks on the curves indicate censored patients. HR indicates hazard ratio; TTFields, tumor-treating fields.

Stupp R Taillibert S Kanner AA et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA.2015 ; 314 (23): 2535 – 2543 .

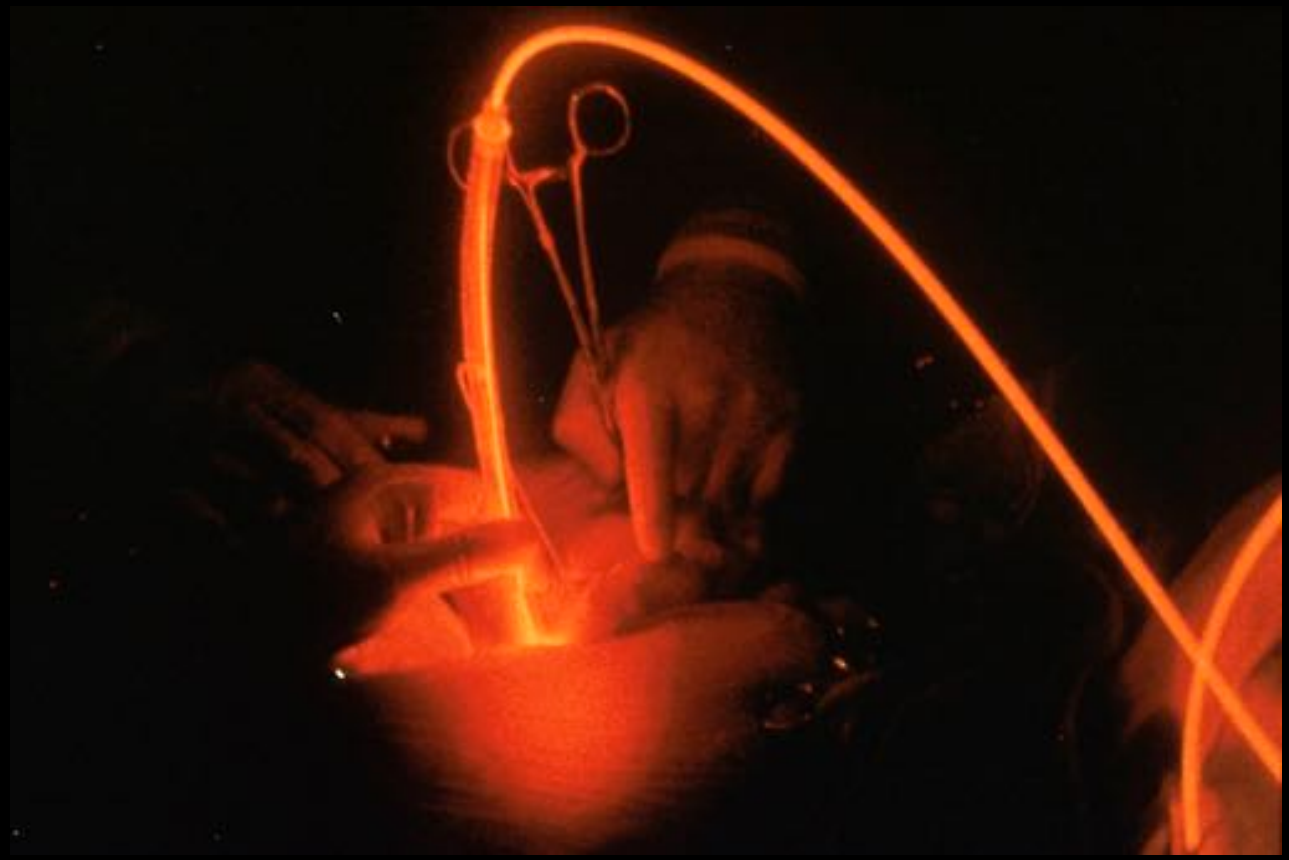
Tumor Treating Fields



Skin toxicities observed under tumor treating fields (TTFields). Some mild-moderate (grade 1–2) skin reaction is observed in up to half of patients (in EF-14 trial reported in 43%, grade 3 in 2%); however, it is usually self-limiting and resolves by removing the electrodes for a few days and applying local steroid-containing ointments. The images represent a few examples of skin reactions. (A) allergic contact dermatitis (B) irritant contact dermatitis (C) folliculitis (D), erosions [Reproduced from ref. 21].

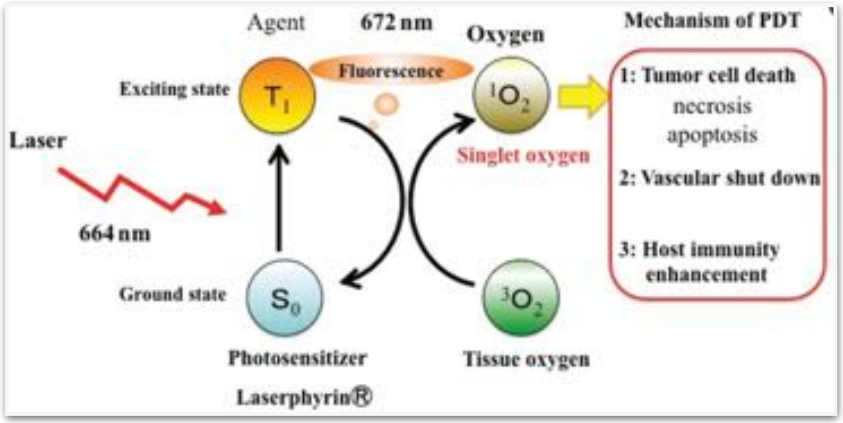
Hottinger, A. F., Pacheco, P., & Stupp, R. (2016). Tumor treating fields: a novel treatment modality and its use in brain tumors. *Neuro-oncology*, *18*(10), 1338-1349.

Photodynamic Therapy

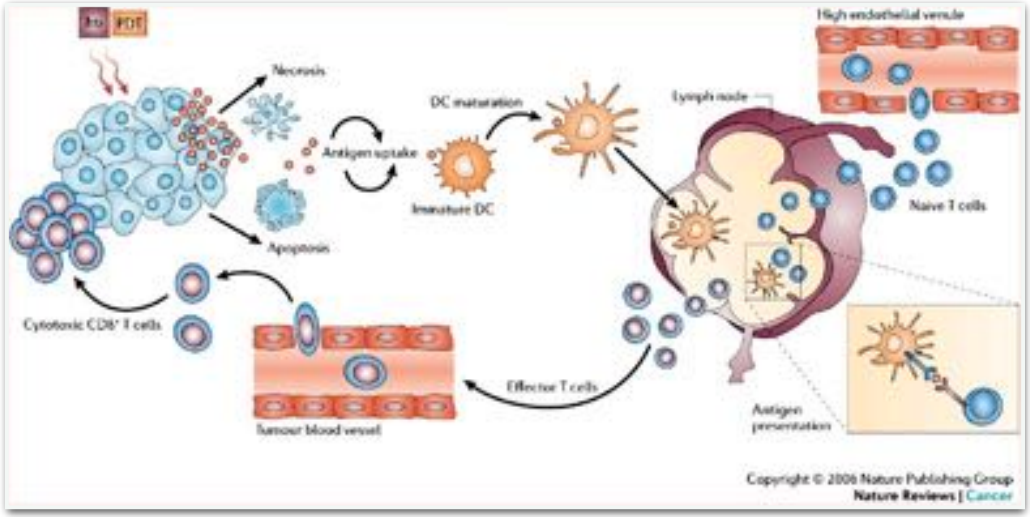


http://www.mindsofmalady.com/2015/08/photodynamic-therapy-advances-offers.html

Photodynamic Therapy

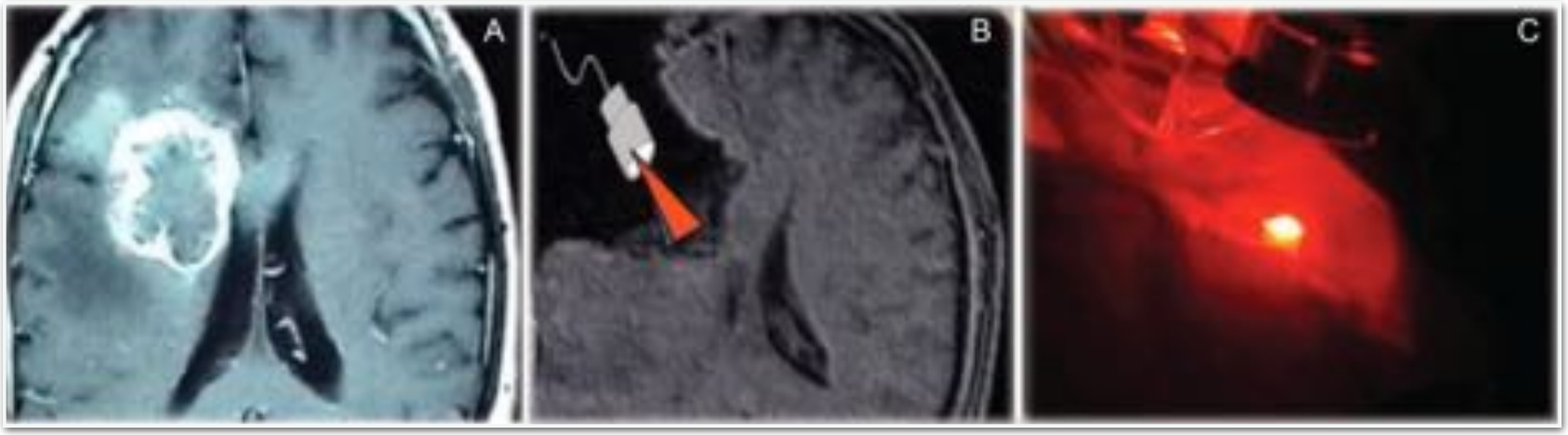


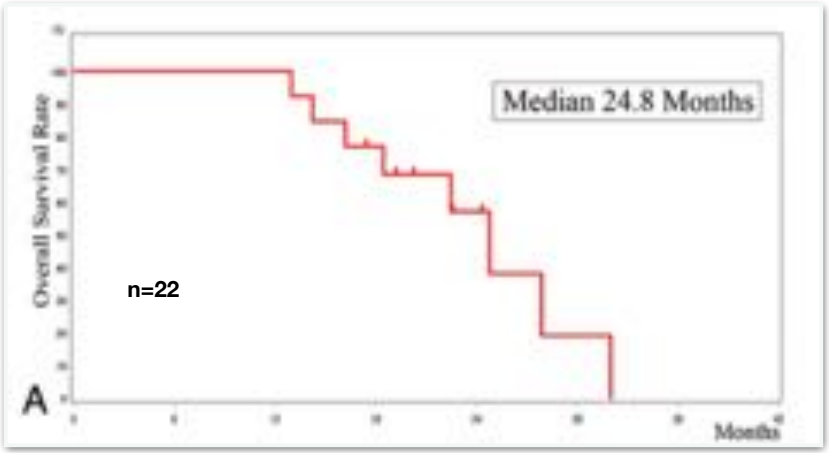
Singlet oxygen is a high-energy form of oxygen.



Akimoto, J. (2016). Photodynamic therapy for malignant brain tumors. *Neurologia medico-chirurgica*, *56*(4), 151-157.

Photodynamic Therapy





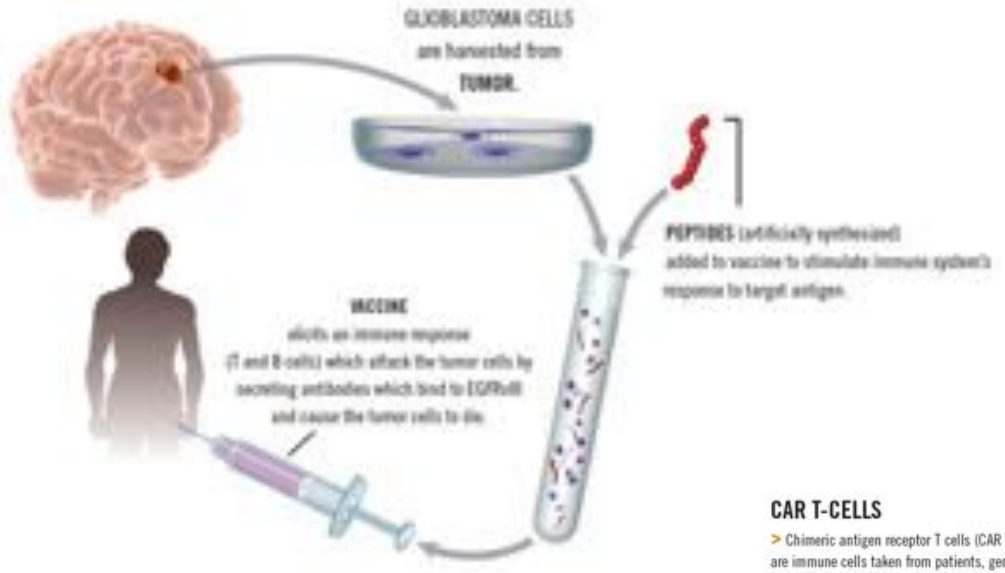
Approved for GBM since 2014 in Japan.

J Neurosurg 119:845–852, 2013
©AANS, 2013

Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors

Akimoto, J. (2016). Photodynamic therapy for malignant brain tumors. *Neurologia medico-chirurgica*, *56*(4), 151-157.

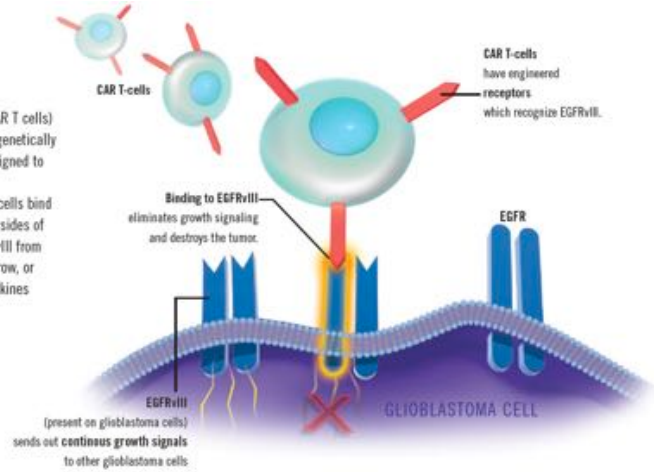
Immunotherapy



CAR T-CELLS

> Chimeric antigen receptor T cells (CAR T cells) are immune cells taken from patients, genetically engineered to include a viral vector designed to seek mutated cells, and reinfused.

> In the body, the engineered immune cells bind to mutated EGFRvIII that sits on the outsides of cancer cells. This either prevents EGFRvIII from signaling surrounding cancer cells to grow, or stimulates immune cells to secrete cytokines that kill the cancer cells.



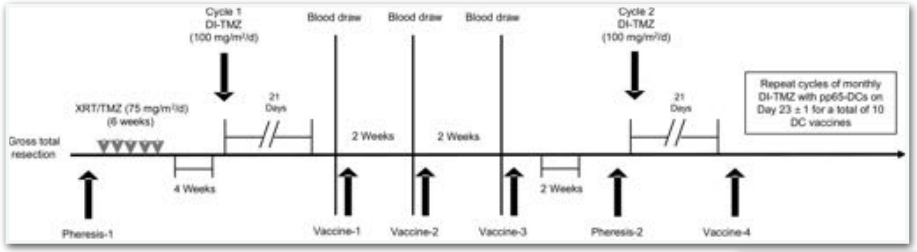
https://www.curetoday.com/publications/cure/2016/winter-2016/comments-from-readers-winter-2016

Immunotherapy

Long-term Survival in Glioblastoma with Cytomegalovirus pp65-Targeted Vaccination

Kristen A. Batich, Elizabeth A. Reap, Gary E. Archer, Luis Sanchez-Perez, Smita K. Nair, Robert J. Schmittling, Pam Norberg, Weihua Xie, James E. Herndon II, Patrick Healy, Roger E. McLendon, Allan H. Friedman, Henry S. Friedman, Darell Bigner, Gordana Vlahovic, Duane A. Mitchell, and John H. Sampson

DOI: 10.1158/1078-0432.CCR-16-2057 Published April 2017



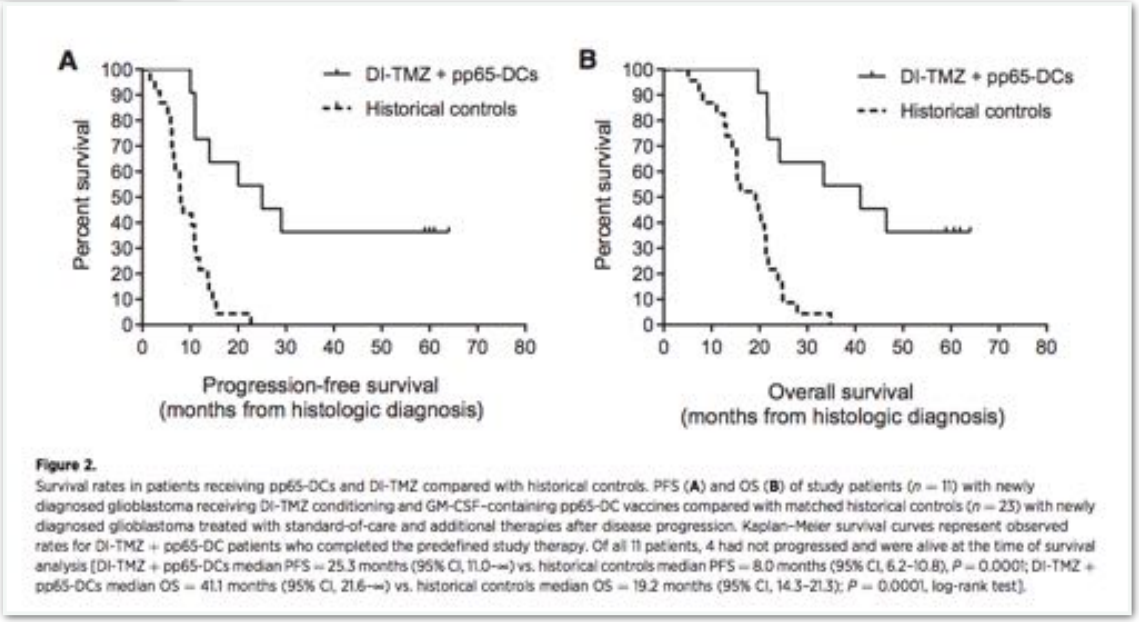
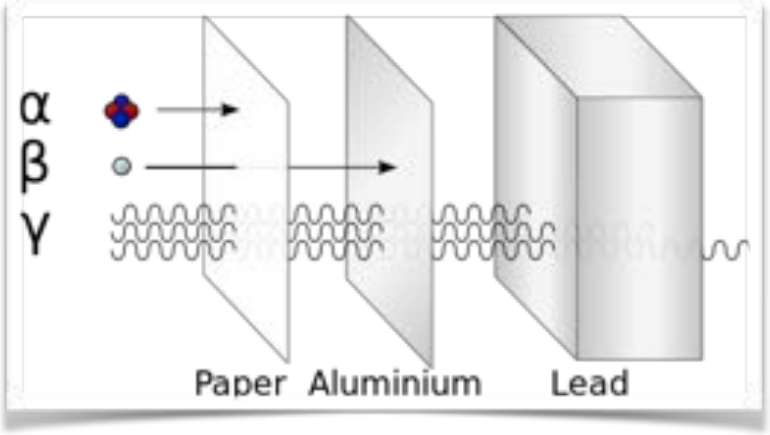
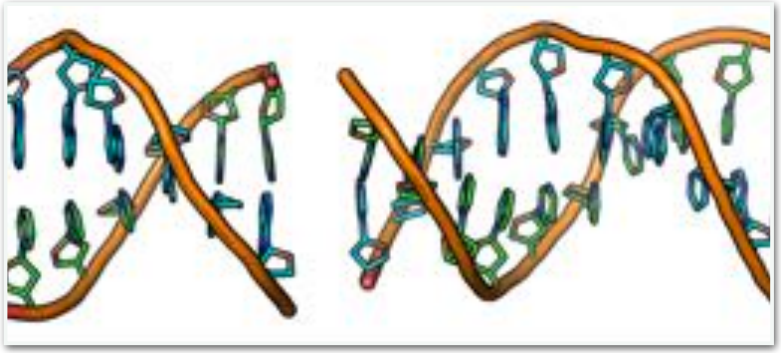


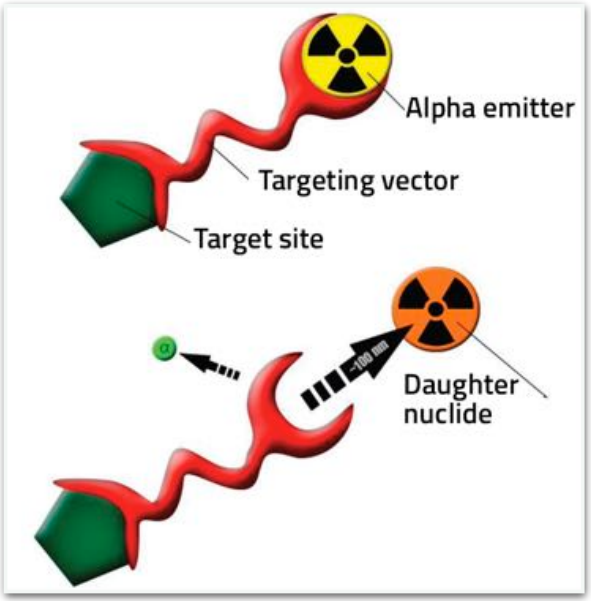
Figure 2.
Survival rates in patients receiving pp65-DCs and DI-TMZ compared with historical controls. PFS (**A**) and OS (**B**) of study patients ($n = 11$) with newly diagnosed glioblastoma receiving DI-TMZ conditioning and GM-CSF–containing pp65-DC vaccines compared with matched historical controls ($n = 23$) with newly diagnosed glioblastoma treated with standard-of-care and additional therapies after disease progression. Kaplan–Meier survival curves represent observed rates for DI-TMZ + pp65-DC patients who completed the predefined study therapy. Of all 11 patients, 4 had not progressed and were alive at the time of survival analysis [DI-TMZ + pp65-DCs median PFS = 25.3 months (95% CI, 11.0–∞) vs. historical controls median PFS = 8.0 months (95% CI, 6.2–10.8), $P = 0.0001$; DI-TMZ + pp65-DCs median OS = 41.1 months (95% CI, 21.6–∞) vs. historical controls median OS = 19.2 months (95% CI, 14.3–21.3); $P = 0.0001$, log-rank test].

Targeted Radiolabeled Compounds



Ionizing Radiation





Targeted Radiolabeled Compounds

^{223}Ra was the first α-emitter approved by the FDA in the United States for treatment of bone metastases from prostate cancer, and is a recommended treatment in the UK by NICE.[3][13] In a phase III trial comparing ^{223}Ra to a placebo, survival was significantly improved.[14]

www.xofigo-us.com

Targeted Radiolabeled Compounds

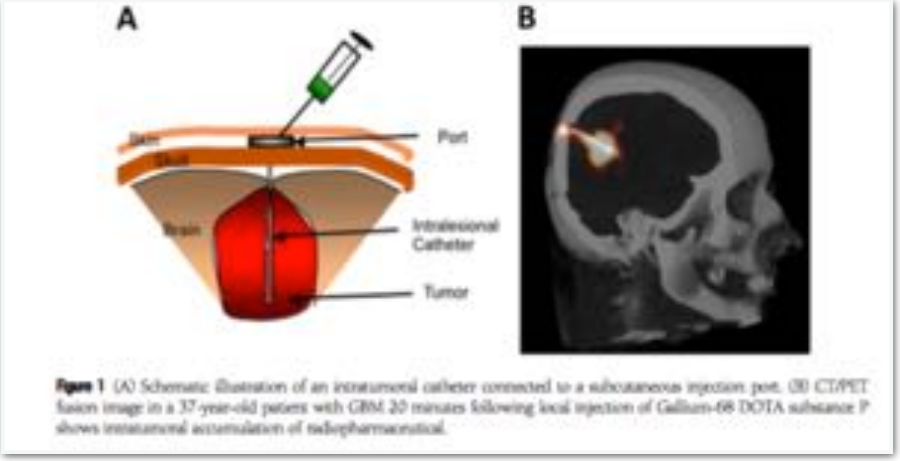


Figure 1 (A) Schematic illustration of an intratumoral catheter connected to a subcutaneous injection port. (B) CT/PET fusion image in a 37-year-old patient with GBM 20 minutes following local injection of Gallium-68 DOTA substance P shows intratumoral accumulation of radiopharmaceutical.

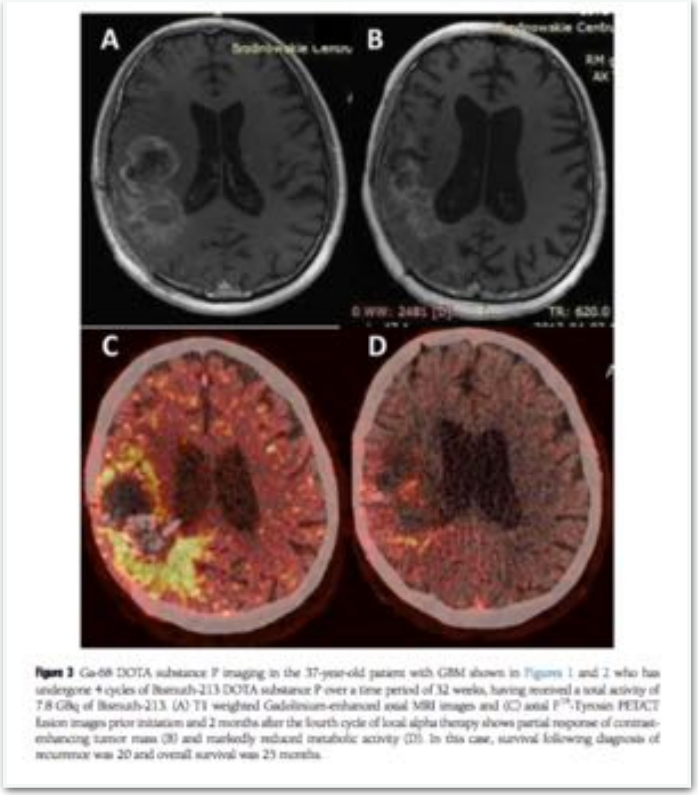


Figure 3 Ga-68 DOTA substance P imaging in the 37-year-old patient with GBM shown in Figures 1 and 2 who has undergone 4 cycles of Bismuth-213 DOTA substance P over a time period of 32 weeks, having received a total activity of 7.8 GBq of Bismuth-213. (A) T1 weighted Gadolinium-enhanced axial MRI images and (C) axial F^{18}-Tyrosin PET/CT fusion images prior initiation and 2 months after the fourth cycle of local alpha therapy shows partial response of contrast-enhancing tumor mass (B) and markedly reduced metabolic activity (D). In this case, survival following diagnosis of recurrence was 20 and overall survival was 23 months.

Cordier, D., Krolicki, L., Morgenstern, A., & Merlo, A. (2016, May). Targeted radiolabeled compounds in glioma therapy. In *Seminars in nuclear medicine*(Vol. 46, No. 3, pp. 243-249). WB Saunders.

Targeted Radiolabeled Compounds

Table 1. Main characteristics of the currently available α-particle-emitting radionuclides.

Isotope	Daughter isotopes*	Physical half-life	Maximum energy (keV)	Occurrence (%)	Associated emissions
^{211}At	–	7.2 h	5.867	α (41.8%)	α, γ, LEE
	^{211}Po	516 ms	7.450	α (100%)	
^{225}Ac	–	10 days	5.830	α (100%)	α, γ, Auger, β⁻
	^{221}Fr	4.9 min	6.341	α (100%)	
	^{217}At	32.3 ms	7.069	α (99.98%)/β⁻ (0.01%)	
	^{213}Bi	45.6 min	6.051	α (2.2%)/ β⁻ (97.8%)	
	^{213}Po	4.2 μs	8.377	α (100%)	
^{213}Bi	–	45.6 min	6.051	α (2.2%)/β⁻ (97.8%)	α, γ, Auger, β⁻
	^{213}Po	4.2 μs	8.377	α (100%)	
^{212}Bi	–	61 min	5.870	α (36%)/β⁻ (64%)	α, γ, Auger, β⁻
	^{212}Po	298 ns	8.785	α (100%)	
^{224}Ra	–	18.72 days	6.038	α (100%)	α, γ, Auger, β⁻
	^{220}Rn	11.4 days	5.871	α (100%)	
	^{216}Po	4 s	6.819	α (100%)	
	^{212}Pb	1.8 ms	7.386	α (100%)	
	^{212}Bi	2.14 min	6.623	α (99.7%)/β⁻ (0.3%)	
^{212}Pb	–	10.64 h		β⁻ (100%)	β⁻
	^{212}Bi	61 min	5.870	α (36%)/β⁻ (64%)	α, γ, Auger, β⁻
	^{212}Po	0.3 μs	8.785	α (100%)	
^{223}Ra	–	11.4 days	5.871	α (100%)	α, γ, Auger, β⁻
	^{219}Rn	4 s	6.819	α (100%)	
	^{215}Po	1.8 ms	7.386	α (100%)	
	^{211}Bi	2.14 min	6.623	α (99.7%)/β⁻ (0.3%)	

*Generated α-particle emitter after decay of the conjugated parent.
LEE: Low-energy electron emission; NS: yield not significant.

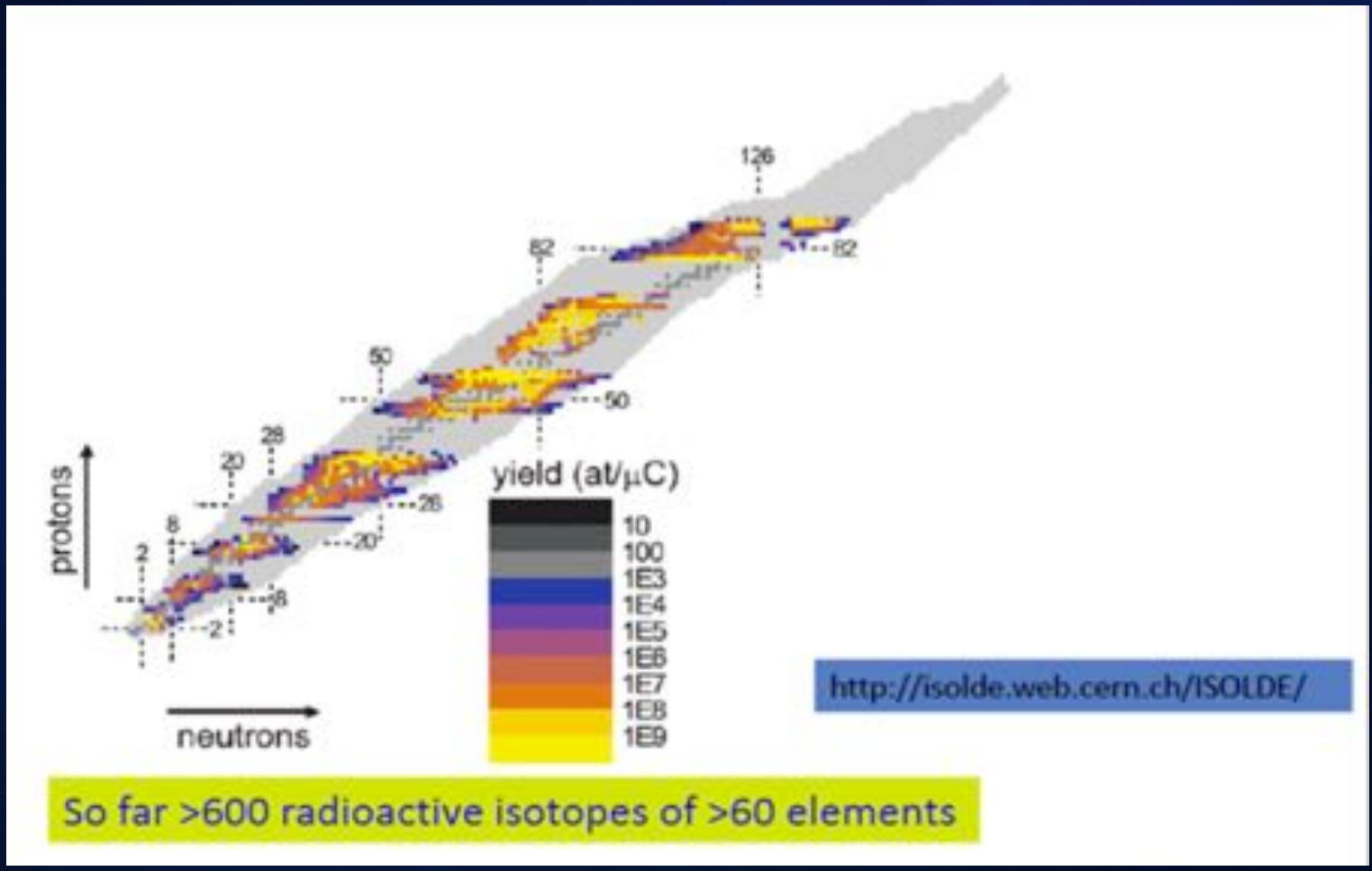
Table 2. Vehicles used in targeted α-particle therapy in preclinical and clinical settings.

Radionuclide	TAT agent	Indication	Antigen	Reference (preclinical data)	Reference (clinical phase)
^{225}Ac	Anti-CD33 IgG (HuM195)	Leukemia	CD33	[18]	I [19,20]
^{225}Ac	Anti-HER2 IgG (trastuzumab)	Ovarian cancer	HER2	[21]	–
^{227}Th	Anti-HER2 IgG (trastuzumab)	Breast and ovarian cancer	HER2	[22,23]	
^{227}Th	Anti-CD20 IgG (rituximab)	Non-Hodgkin lymphoma	CD20	[24,25]	
^{213}Bi	Anti-CD33 IgG (HuM195)	Leukemia	CD33	[26,27]	I and I/II [28,29]
^{213}Bi	Anti-CD20 IgG (rituximab)	Non-Hodgkin lymphoma	CD20	[30,31]	I [32]
^{213}Bi	Plasminogen activator inhibitor type 2	Breast cancer, pancreatic cancer	Urokinase plasminogen activator receptor	[33–35]	
^{213}Bi	Anti-MUC1 IgG (C595 IgG)	Ovarian cancer, pancreatic cancer	MUC1	[36,37]	
^{213}Bi	Substance P	Glioblastoma	Neurokinin type-1 receptor		0/I [38,39]
^{213}Bi	Anti-NG2 IgG (9.2.27 IgG)	Melanoma	NG2 proteoglycan	[40,41]	I [15,42,43]
^{213}Bi	Anti-CD138 IgG	Multiple myeloma	CD138	[44]	
^{213}Bi	Anti-PSMA IgG (J591 IgG)	Prostate cancer	PSMA	[45]	
^{213}Bi	C6.5K-A scFv, C6.5K-A diabody	Breast and ovarian carcinomas	HER2	[46]	
^{212}Pb/^{212}Bi	Anti-HER2 IgG (TCMC-trastuzumab)	Ovarian cancer	HER2	[47,48]	[48–50]
^{211}At	Chimeric 81C6 IgG	Glioblastoma	Tenascin-C	[51,52]	II [53]
^{211}At	MX35 F(ab')$_2$	Ovarian cancer	NaPi2b	[54]	I [55]
^{211}At	Anti-FRA IgG (Mov18)	Ovarian cancer	Folate receptor alpha	[56]	
^{211}At	Anti-EGFRvIII IgG	Glioblastoma	EGFRvIII	[57]	
^{211}At	Anti-HER2 C6.5 diabody	Breast cancer	HER2	[58]	
^{211}At	$Z_{HER2:342}$ and $(Z_{HER2:342})_2$ affibody molecules	Breast and ovarian carcinomas	HER2	[59]	
^{223}Ra	^{223}Ra-chloride	Skeletal breast and prostate cancer metastases	Hydroxyapatite	[60]	I–III [61,62]

NG2: Neural/glial antigen 2; PSMA: prostate-specific membrane antigen; EGFRvIII: epidermal growth factor receptor variant III.

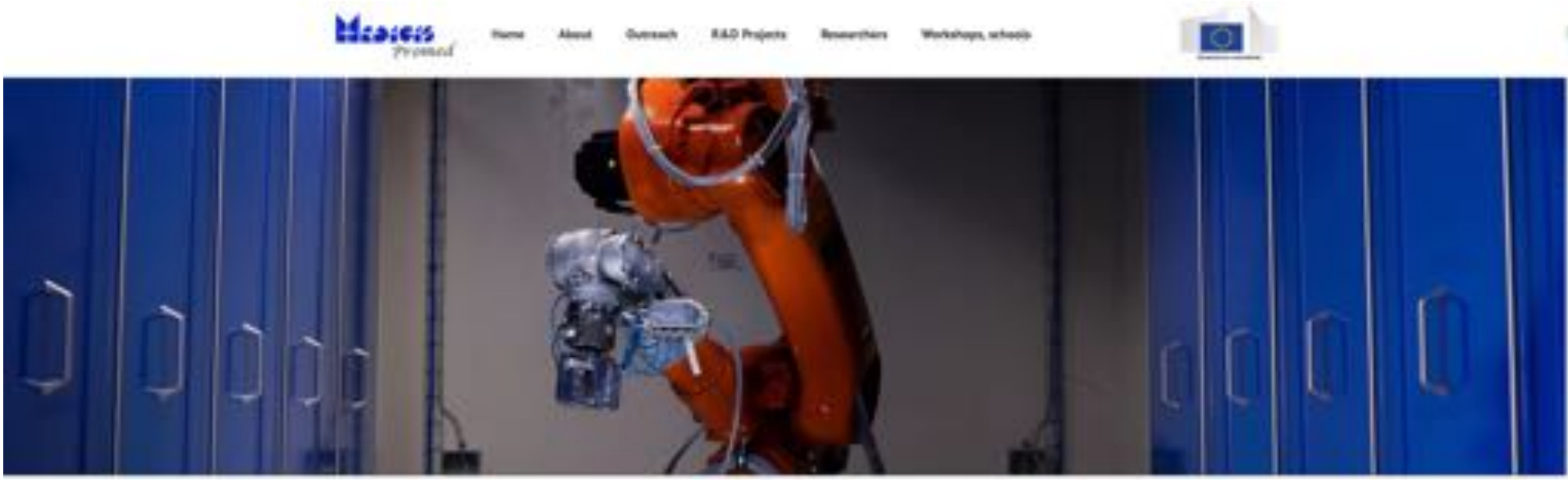
Dekempeneer, Y., Keyaerts, M., Krasniqi, A., Puttemans, J., Muyldermans, S., Lahoutte, T., ... & Devoogdt, N. (2016). Targeted alpha therapy using short-lived alpha-particles and the promise of nanobodies as targeting vehicle. *Expert opinion on biological therapy*, *16*(8), 1035-1047.

CERN - Isolde



Largest range of available isotopes worldwide

CERN Medicis



https://home.cern/about/updates/2013/09/cern-produce-radioisotopes-health

Orthotopic GBM

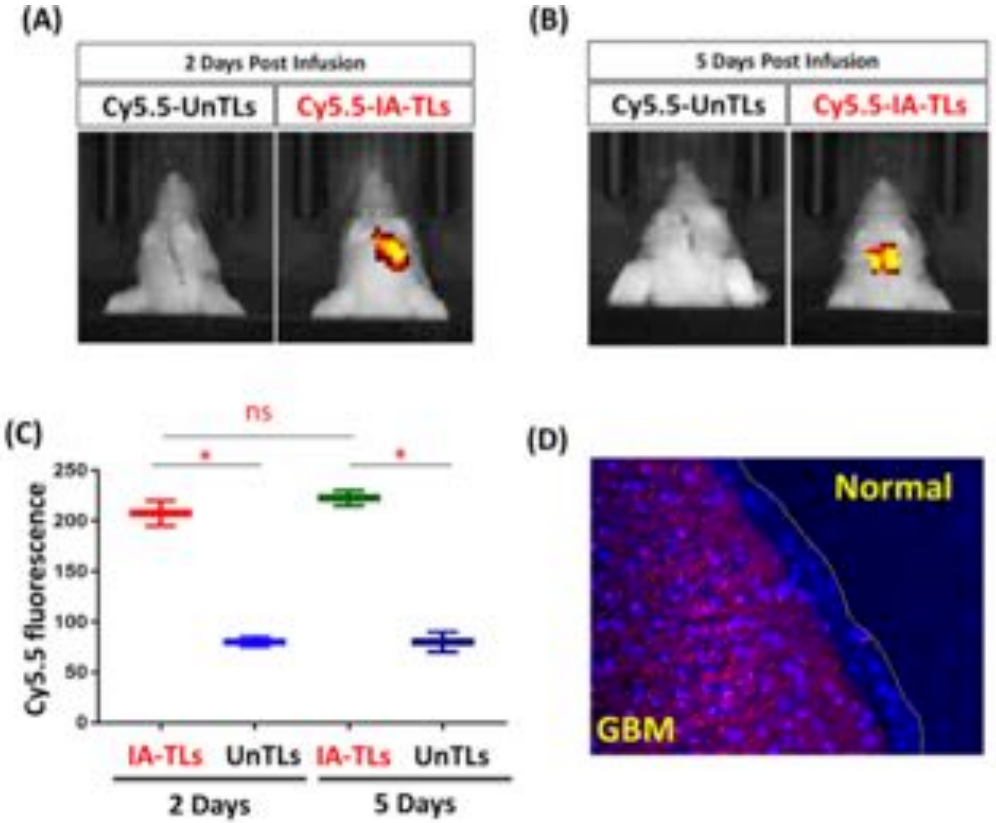
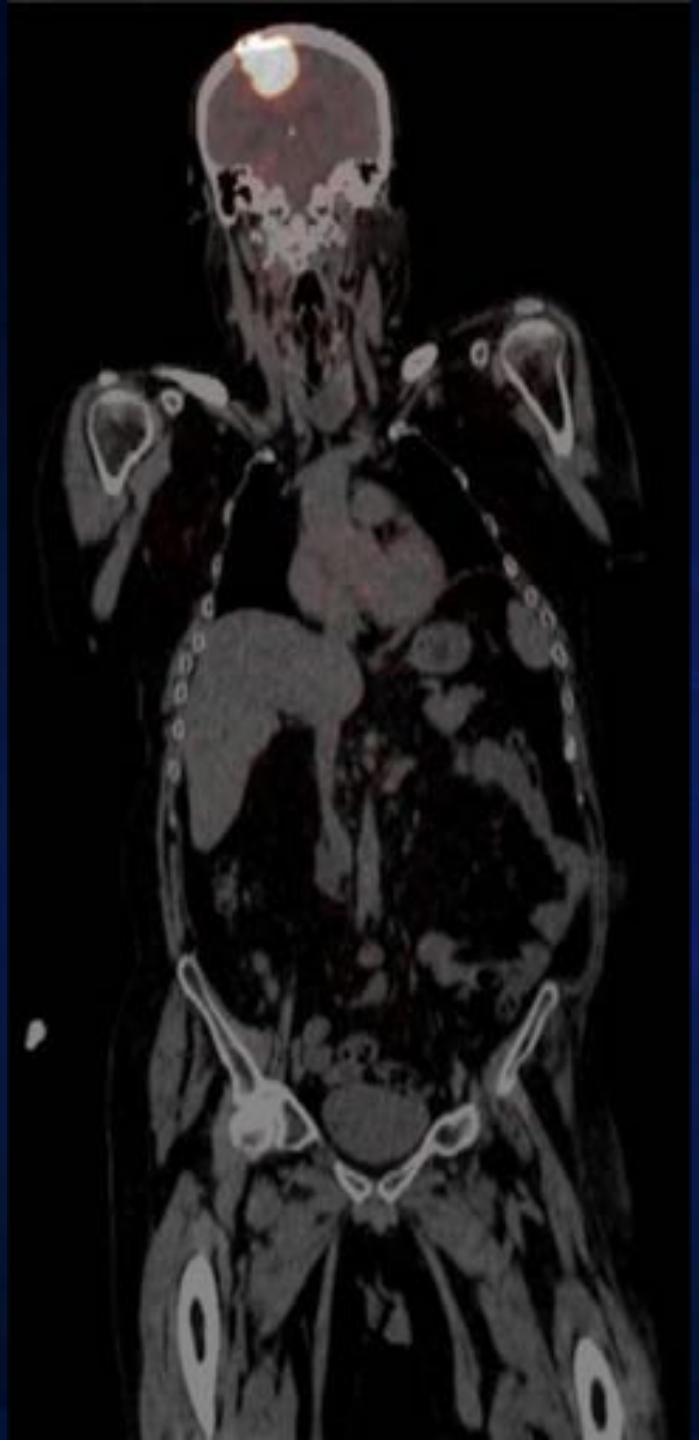


Figure 2: in vivo specificity of cy5.5-IA-TLs towards $\alpha_v\beta_3$. in vivo fluorescence imaging showing tumor accumulation of intracranially infused cy5.5 labeled $\alpha_v\beta_3$ targeted nanoparticles (cy5.5-IA-TL) (n=3) and cy5.5 labeled untargeted nanoparticles (n=3) (cy5.5-UnTLs) 2 days (n=3) (A) and 5 days (n=3) (B) post intracranial infusion. (C) Cy5.5-IA-TLs accumulated within GBM tissue significantly greater than cy5.5- UnTLs 2 days and 5 days post intracranial infusion. (D) Brain sections from mice revealed Cy5.5-IA-TLs to be abundant within GBM tissue. Negligible presence of cy5.5-IA-TLs was found within normal regions of the brain surrounding GBM tissue. Data represented as mean +/- SEM. Student's t-test was performed to assess difference between experimental groups (*$p< 0.05$(significant); ns= not significant).

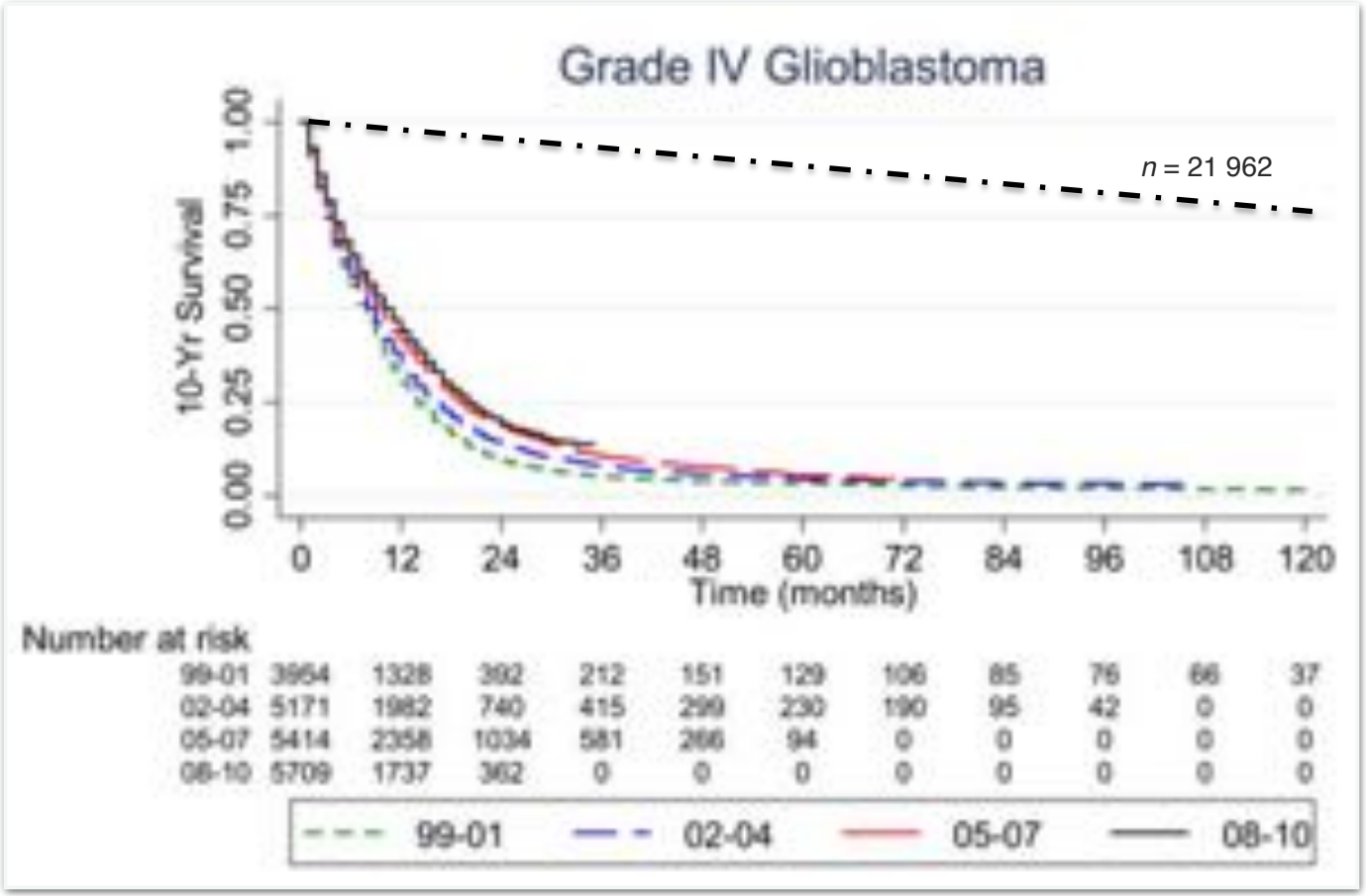
Alpha particle enhanced Blood Brain/Tumor Barrier permeabilization in glioblastomas using integrin alpha-v beta-3 targeted liposomes DOI: 10.1158/1535-7163.MCT-16-0907



Cordier, D., Krolicki, L., Morgenstern, A., & Merlo, A. (2016, May). Targeted radiolabeled compounds in glioma therapy. In *Seminars in nuclear medicine*(Vol. 46, No. 3, pp. 243-249). WB Saunders.

Glioblastma

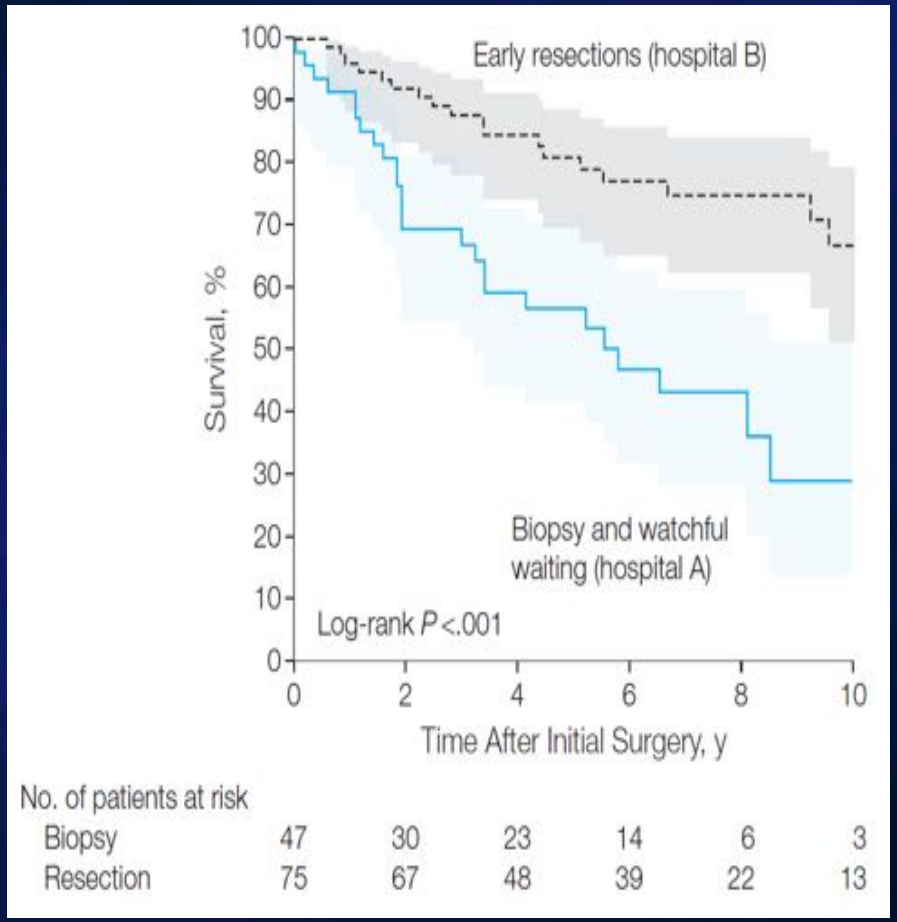
Survival



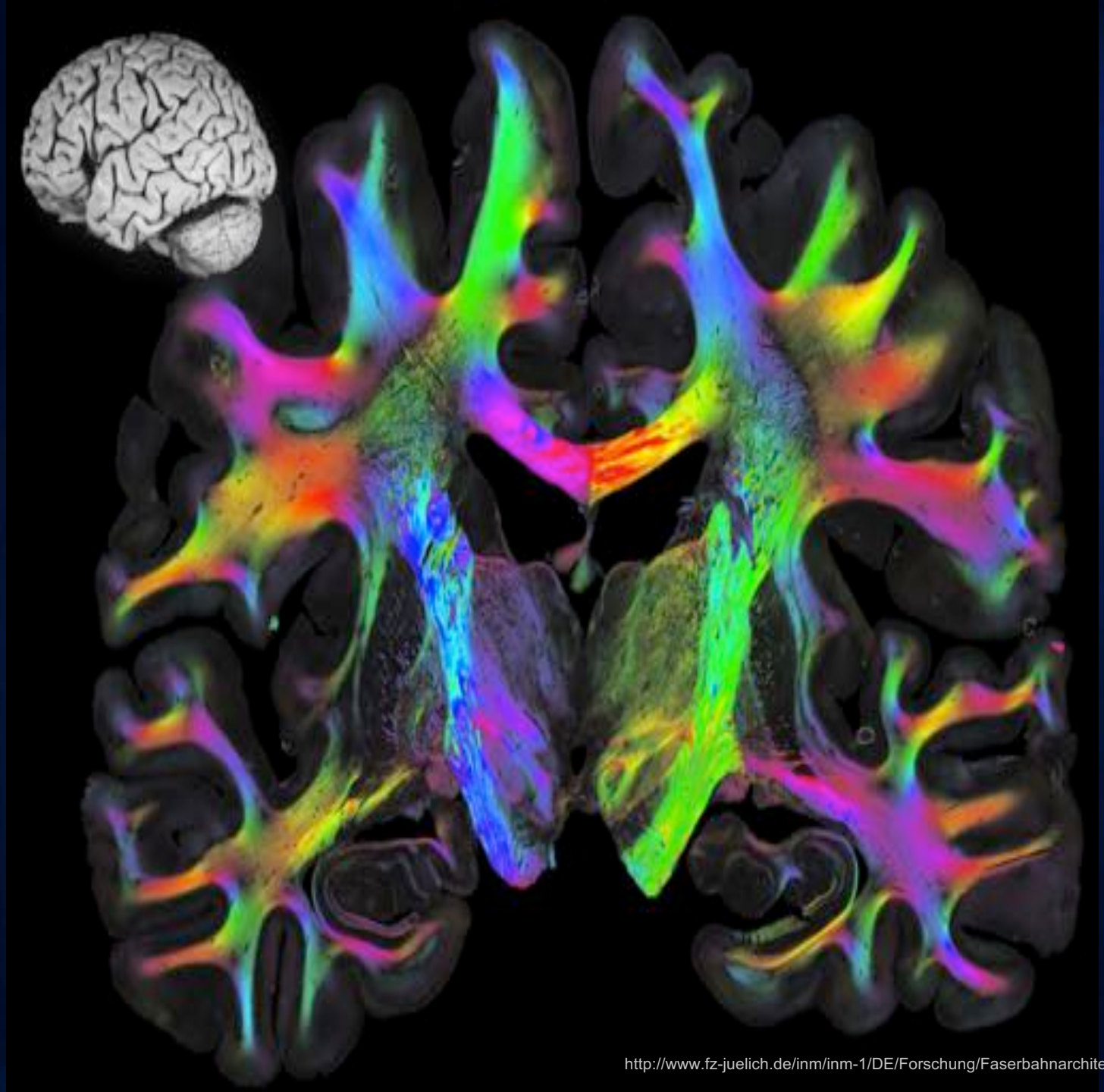
Survival trends of grade I, II, and III astrocytoma patients and associated clinical practice patterns between 1999 and 2010: A SEER-based analysis
Xuezhi Dong et al., Neuro-Oncology Practice 3(1), 29–38, 2016

Challenge:
to visualize the
true tumor extension

Timing of surgery vs. scan and wait



Jakola et al. Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low grade gliomas. JAMA 308:1-8, 2012



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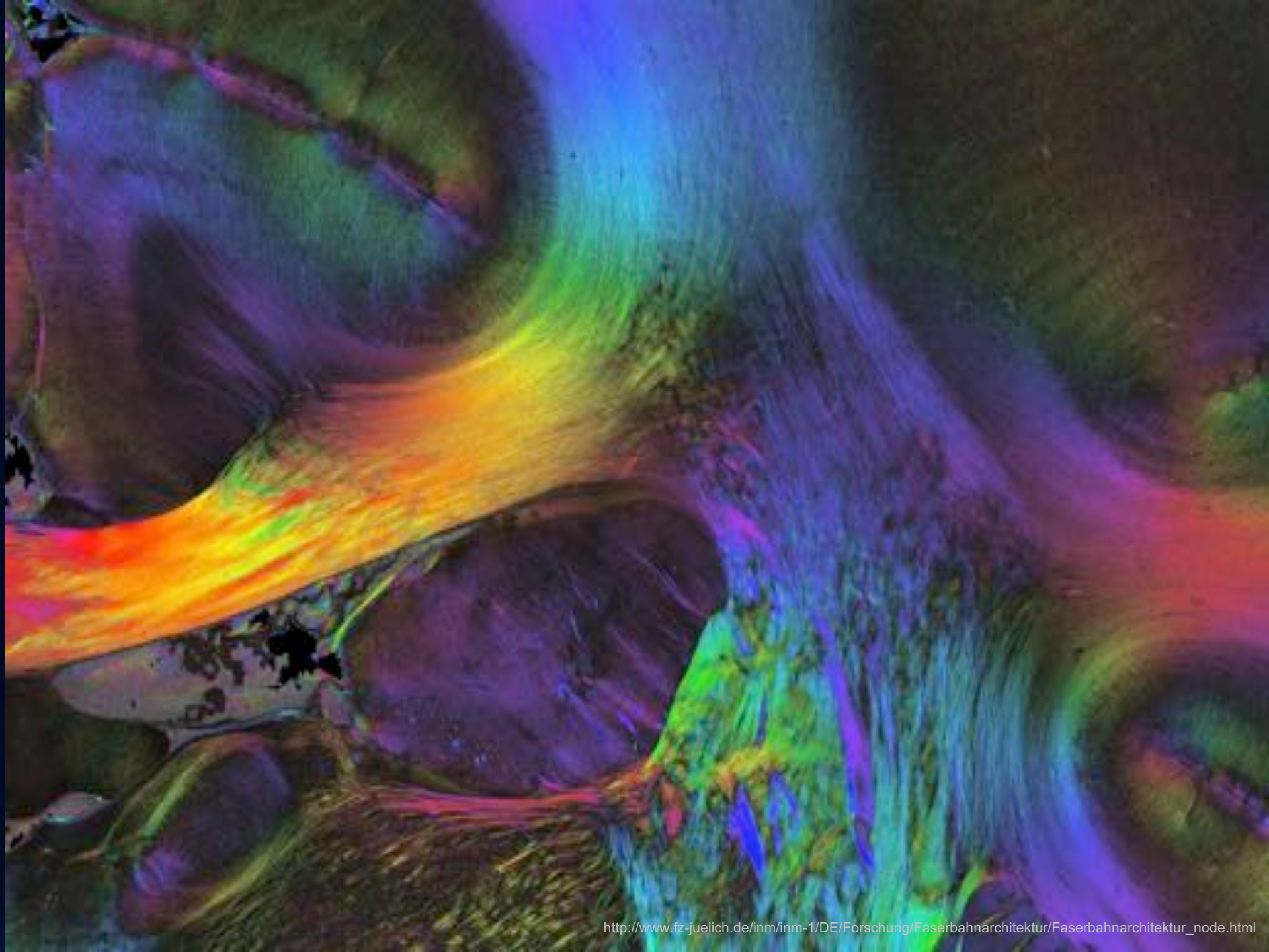

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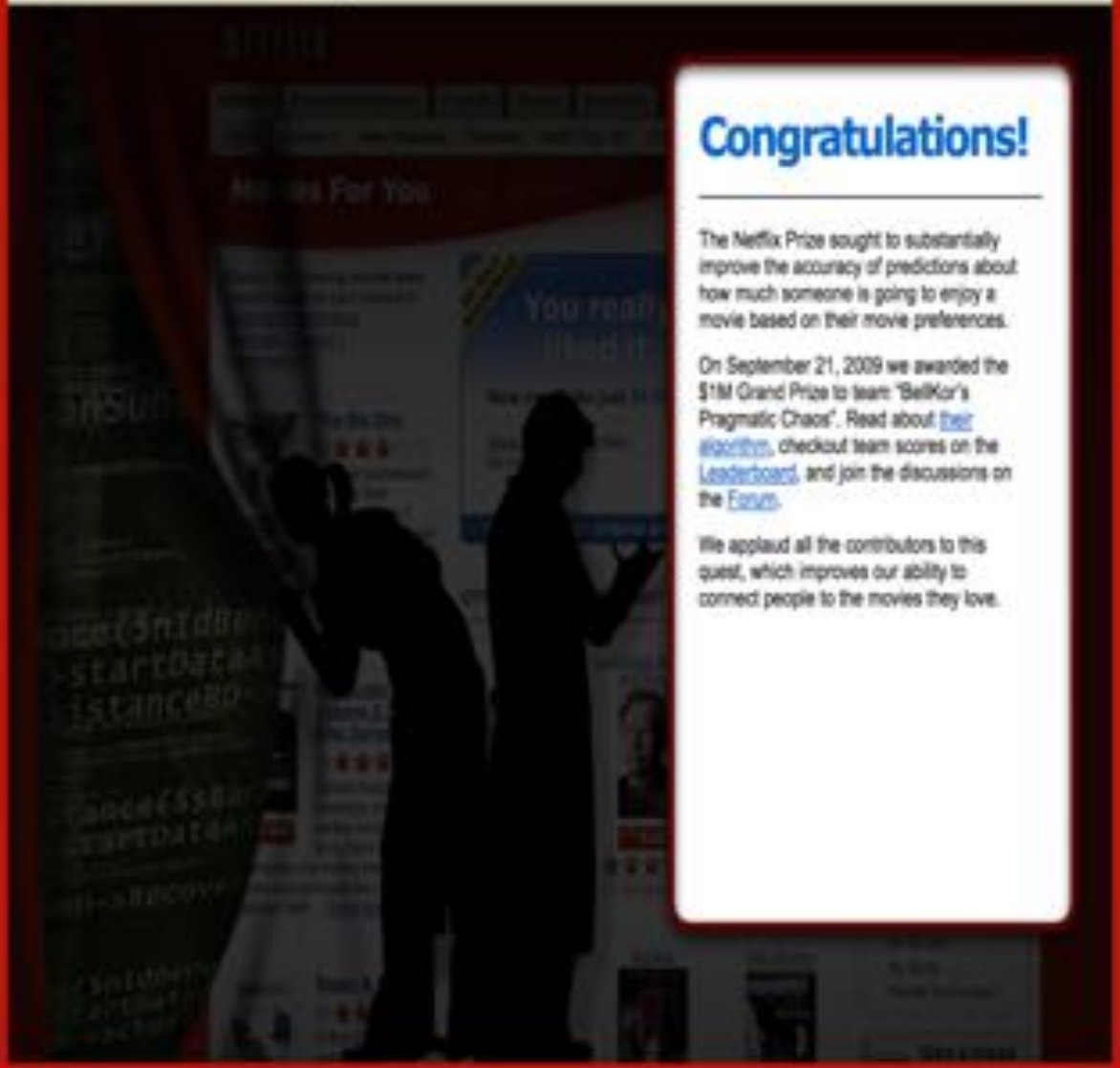
NETFLIX

Netflix Prize

COMPLETED

Home Rules Leaderboard Update

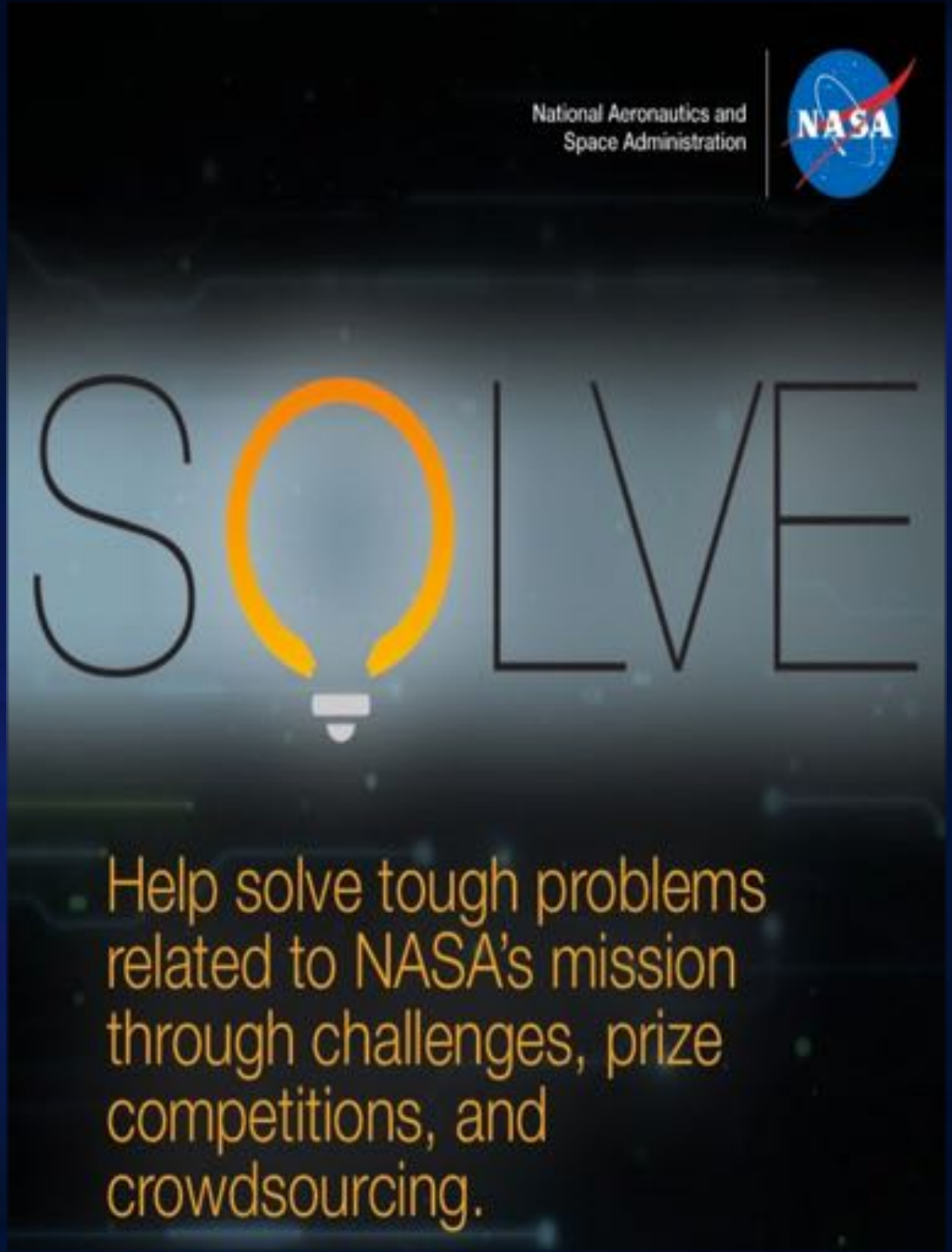


Congratulations!

The Netflix Prize sought to substantially improve the accuracy of predictions about how much someone is going to enjoy a movie based on their movie preferences.

On September 21, 2009 we awarded the $1M Grand Prize to team "BellKor's Pragmatic Chaos". Read about their algorithm, checkout team scores on the Leaderboard, and join the discussions on the Forum.

We applaud all the contributors to this quest, which improves our ability to connect people to the movies they love.


National Aeronautics and
Space Administration
NASA
SOLVE
Help solve tough problems
related to NASA's mission
through challenges, prize
competitions, and
crowdsourcing.

HORAO

„The verb horao is common from Homer onwards and in the active means, “to see with your mind” (Homer, Odyssey, 4, 540). „

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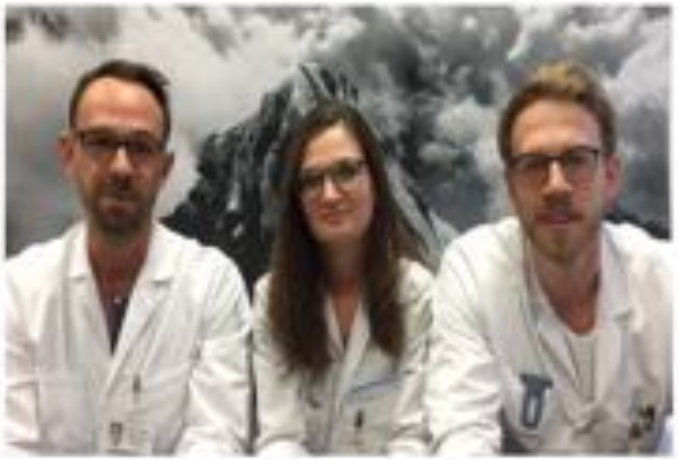
Crowdfunding

Raise Awareness & Prize-Money

What we do

The HORAO project asks the most brilliant minds to develop new technologies, that will help visualize the exact border between the tumor and the healthy brain tissue during brain tumor surgery.

Surgery is the crucial treatment step for most patients with brain tumors. A clear identification of the fine border between the tumor and the surrounding brain is essential in order to radically resect the tumor and to preserve neurological function. However, while easy to identify in preoperative MRI, solid tumor tissue is often difficult to differentiate from infiltrated white matter during surgery.



What we need

Our goal is to improve delineation of brain tumors during surgery. Instead of focusing on the difficult to detect tumor itself, we focus on identifying healthy white matter by means of its tracts.

The brains entire white matter is made up of fiber tracts that comprise bundles of axons. This high degree of structure in

This project ended successfully on 18/9/2017 17:00!

Rewards

CHF	20.-	48 taken
Thank You Postcard		
CHF	20.-	7 / 222 taken
20min-Laser Spende		
CHF	75.-	8 / 30 taken
Visit to the Artstudio		
CHF	99.-	27 taken
Band-aid!		
CHF	125.-	6 / 25 taken
Führung		
CHF	160.-	29 / 50 taken
T-Shirt		
CHF	200.-	9 / 25 taken
«Do No Harm»		
CHF	250.-	15 / 35 taken
Join the Conference		
CHF	777.-	9 / 17 taken
Masterclass of Neurosurgery		

Crowdsourcing

Worldwide Prize-Based Competition

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Thank you!



Bern, Switzerland