Limits of Radical Resection for Low- and High-Grade Gliomas

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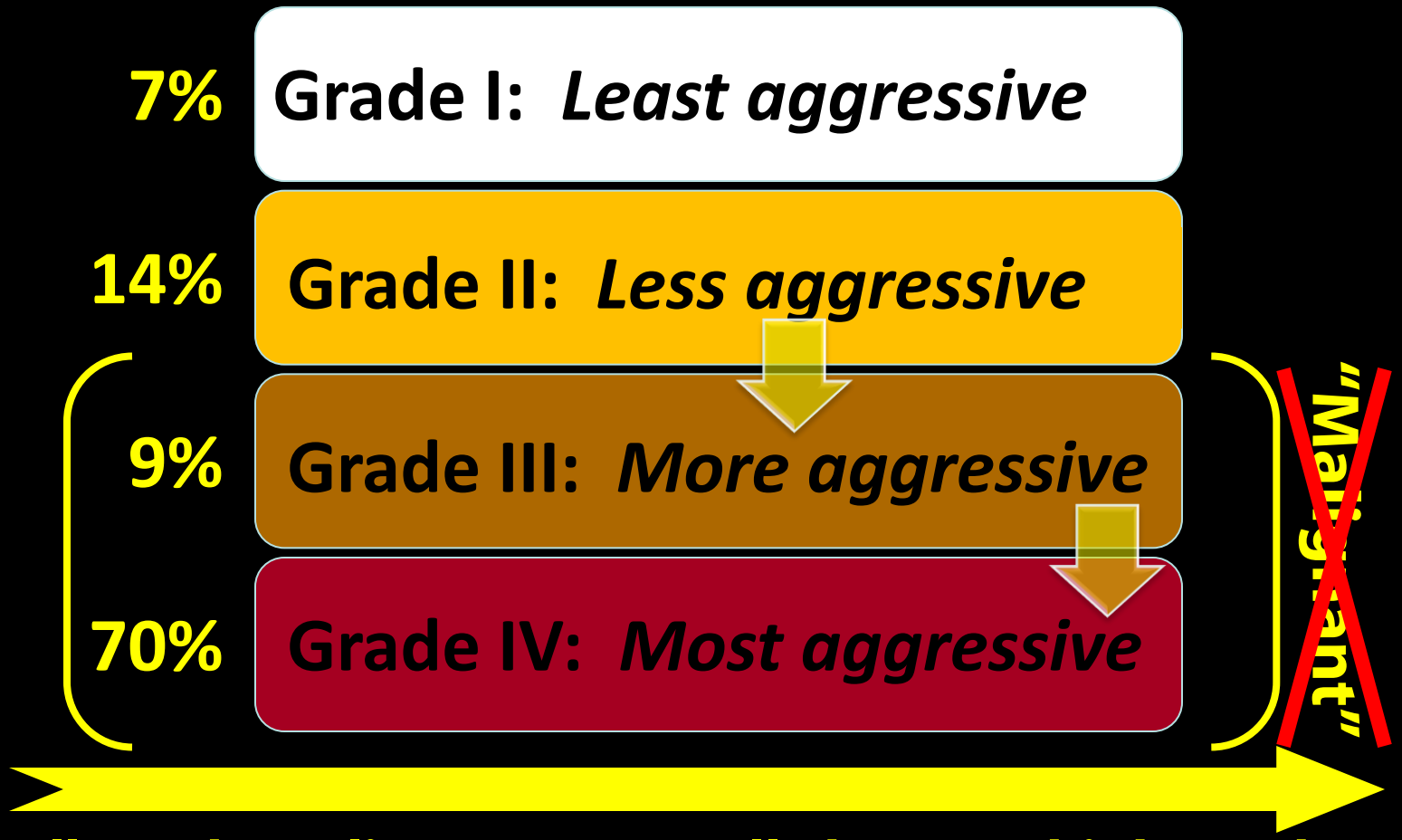
Disclosures

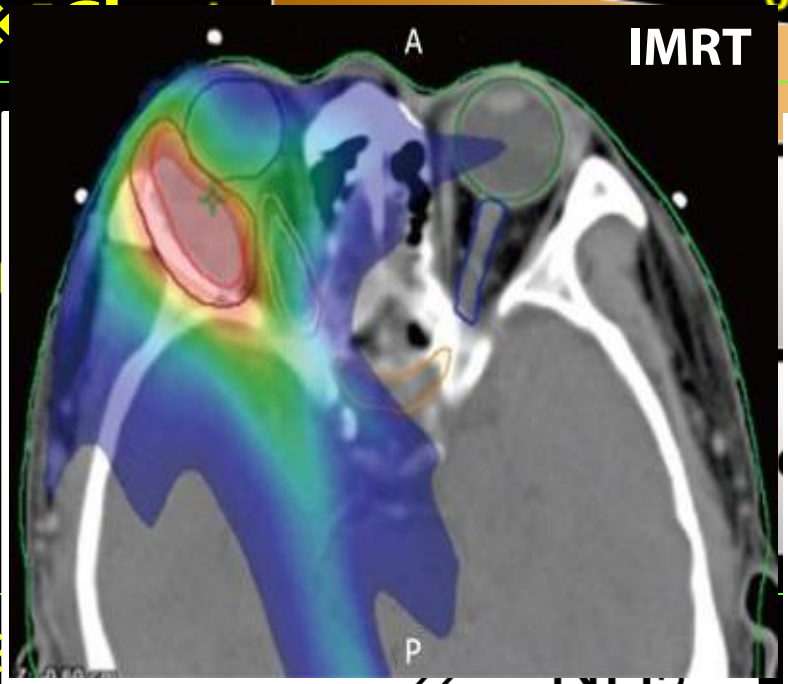
EXTRAMURAL RESEARCH SUPPORT	American Association of Neurological Surgeons American Brain Tumor Organization American Cancer Society American Society of Clinical Oncology Arizona Biomedical Research Commission National Cancer Institute National Institute of Neurological Disorders and Stroke Novartis AG The Ben & Catherine Ivy Foundation The Pivotal Foundation The Thurston Foundation
ADVISORY BOARDS	Caris Life Sciences Carl Zeiss AG Medtronic, Inc. Osteomed L.P.

Distribution of Adult Gliomas



Current Glioma Standards of Care

- Surgery
- Radiation Therapy
- Chemotherapy



Current Glioma Survival Data from the U.S.

	Mean Age at Diagnosis	2-Year Survival	5-Year Survival	10-Year Survival
Grade I	17	91%	88%	84%
Grade II	40	55%	45%	35%
Grade III	42	40%	25%	20%
Grade IV	55	12%	5%	3%

Source: 2014 Central Brain Tumor Registry of U.S.

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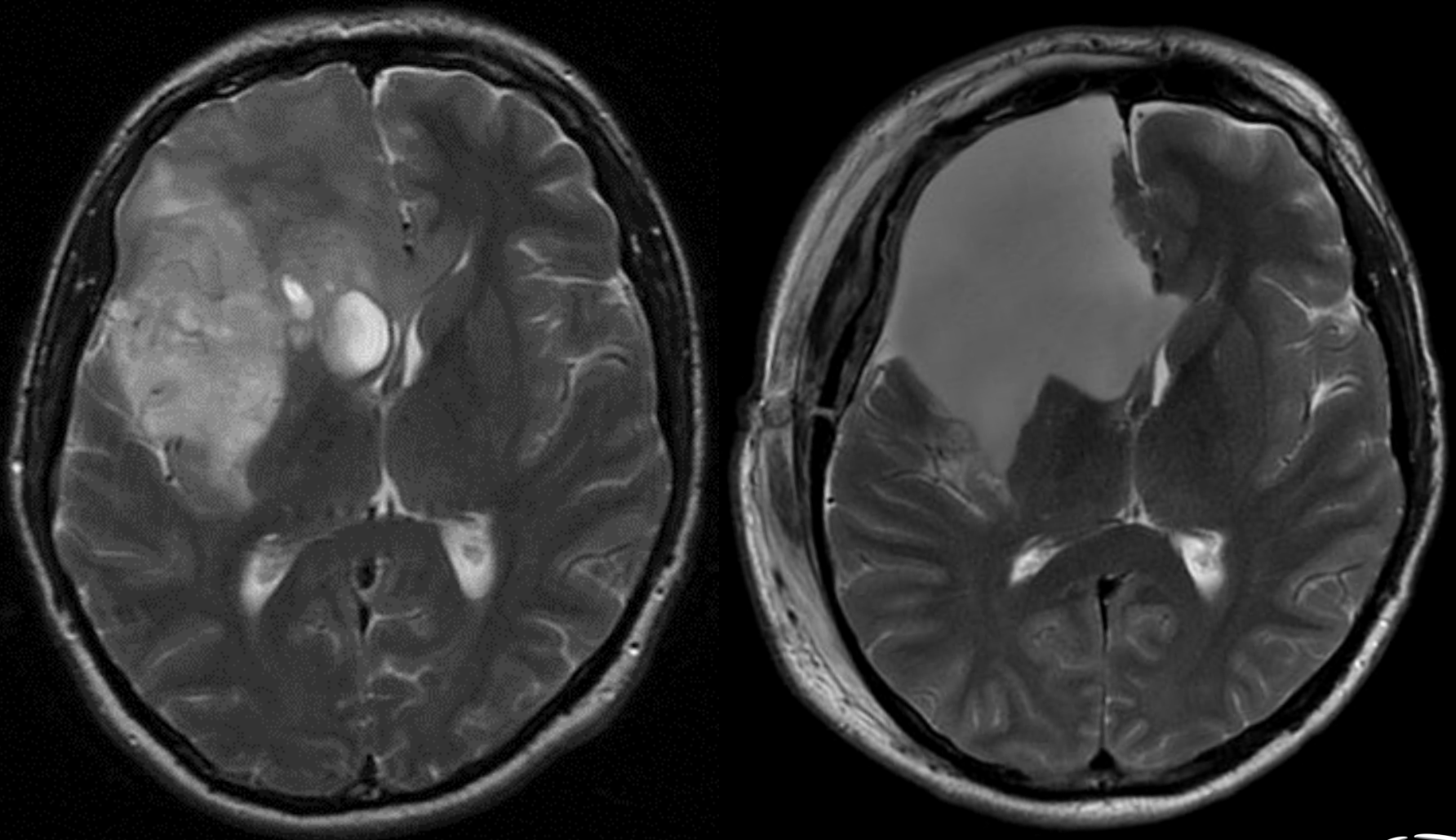
Low-Grade Gliomas: Extent of Resection



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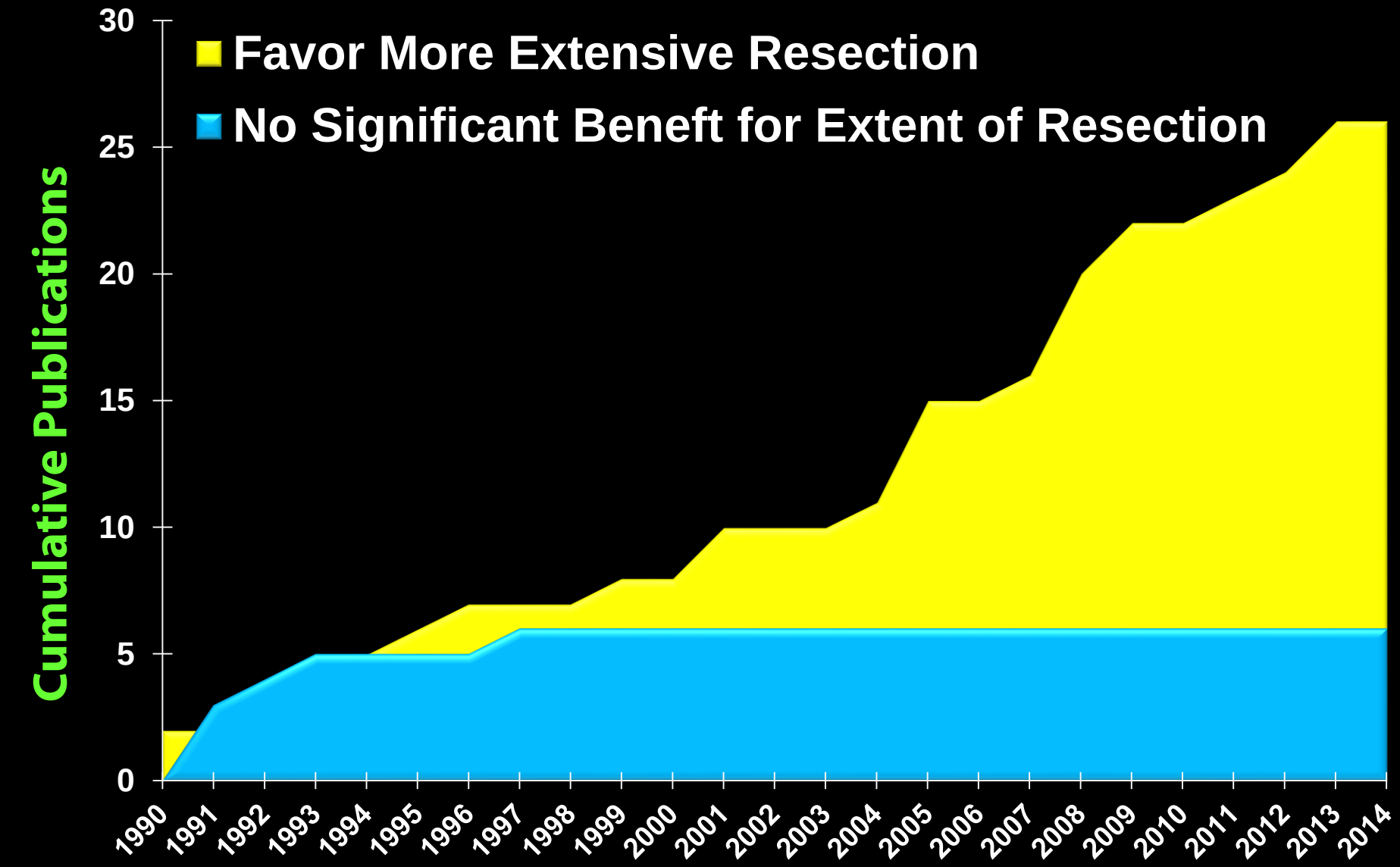
LGG Surgery in the Modern Literature



The Value of Extent of Resection: Low-Grade Glioma Overall Survival

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

Smith *et al*.

J Clin Oncol. 2008; 26(8):1338-45

n = 216		Hazard Ratio	
	P	Point Estimate†	95% CI

EOR remained significant predictor of overall survival even if only analyzing patients with EOR ≥ 80%

* Adjusted for the effects of patient age, KPS, tumor location and tumor subtype.

† Per unit of measure (e.g. log cm^3, cm^3, %)

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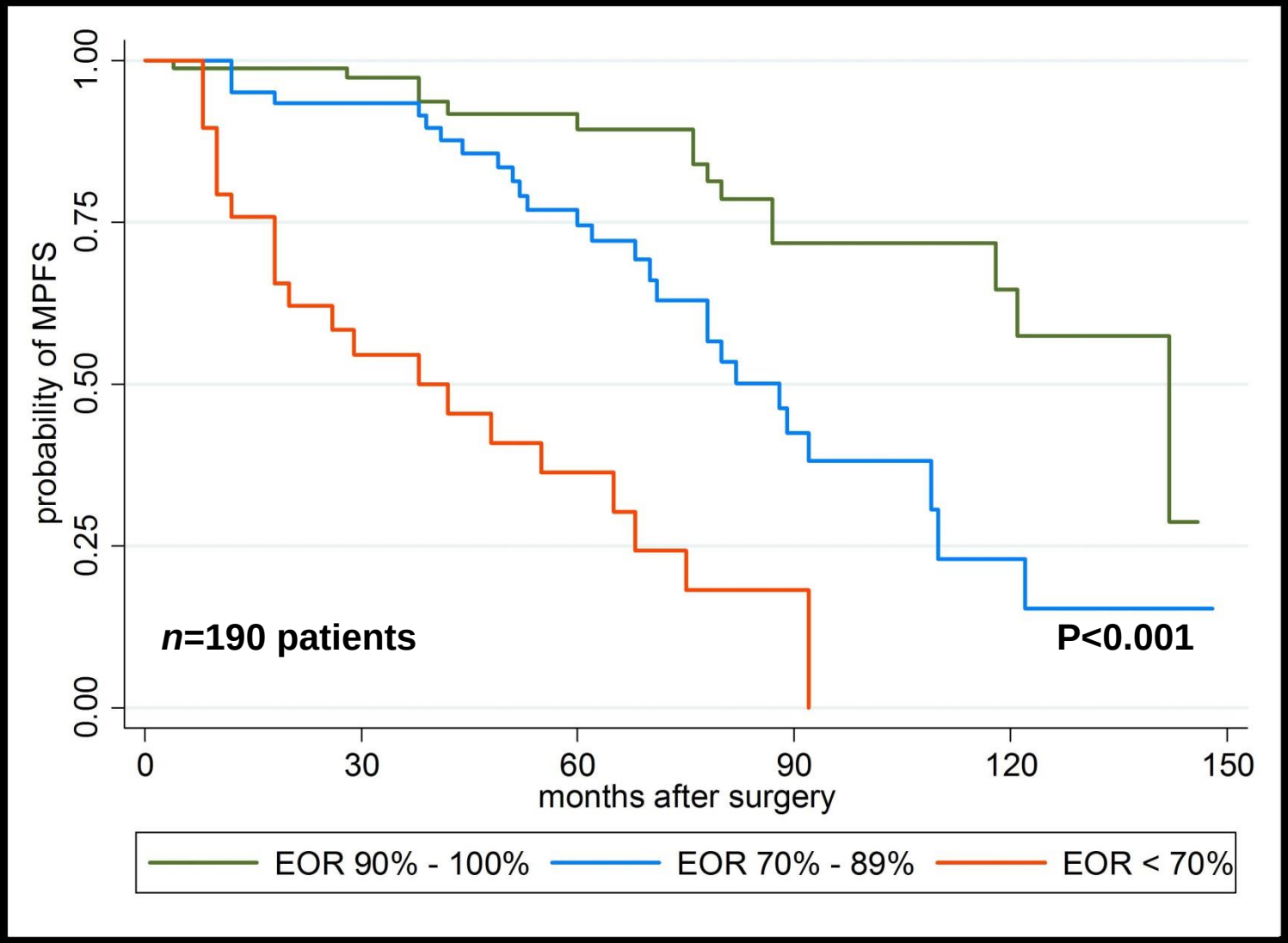
The Value of Extent of Resection: Low-Grade Glioma Transformation



Ius *et al*, *J. Neurosurg.* 2012; 117:1039-1052

Low-Grade Glioma Heterogeneity

	Median Age at Diagnosis	2-Year Survival	5-Year Survival	10-Year Survival
Grade I *JPA*	17	97%	94%	91%
Grade II *Astrocytoma*	40	61%	47%	35%
Grade II *Oligodendroglioma*	32	90%	79%	64%
Grade II *Mixed Glioma*	35	75%	57%	46%

Source: 2014 Central Brain Tumor Registry of U.S.

Low-Grade Glioma Heterogeneity

World Health Organization (WHO) Grade I

Juvenile Pilocytic Astrocytoma (JPA)
Subependymal Giant Cell Astocytoma (SEGA)
Myxopapillary Ependymoma
Subependymoma
Dysembryoplastic Neuroepithelial (DNET)
Ganglioglioma
Choroid Plexus Papilloma

WHO Grade II

Diffuse Astrocytoma
Oligodendroglioma
Oligoastrocytoma
Pleiomorphic Xanthroastrocytoma
Pilomyxoid Astrocytoma
Ependymoma
Central Neurocytoma

Low-Grade Glioma Heterogeneity

Astrocytomas

World Health Organization (WHO) Grade I

- Juvenile Pilocytic Astrocytoma (JPA)
- Subependymal Giant Cell Astocytoma (SEGA)
- Myxopapillary Ependymoma
- Subependymoma
- Dysembryoplastic Neuroepithelial (DNET)
- Ganglioglioma
- Choroid Plexus Papilloma

Oligodendrogliomas

Mixed Gliomas

WHO Grade II

- Diffuse Astrocytoma
- Oligodendroglioma
- Oligoastrocytoma
- Pleomorphic Xanthroastrocytoma
- Pilomyxoid Astrocytoma
- Ependymoma
- Central Neurocytoma

Glioma with Ependymal Differentiation

Others

LGG Heterogeneity: Oligodendrogliomas

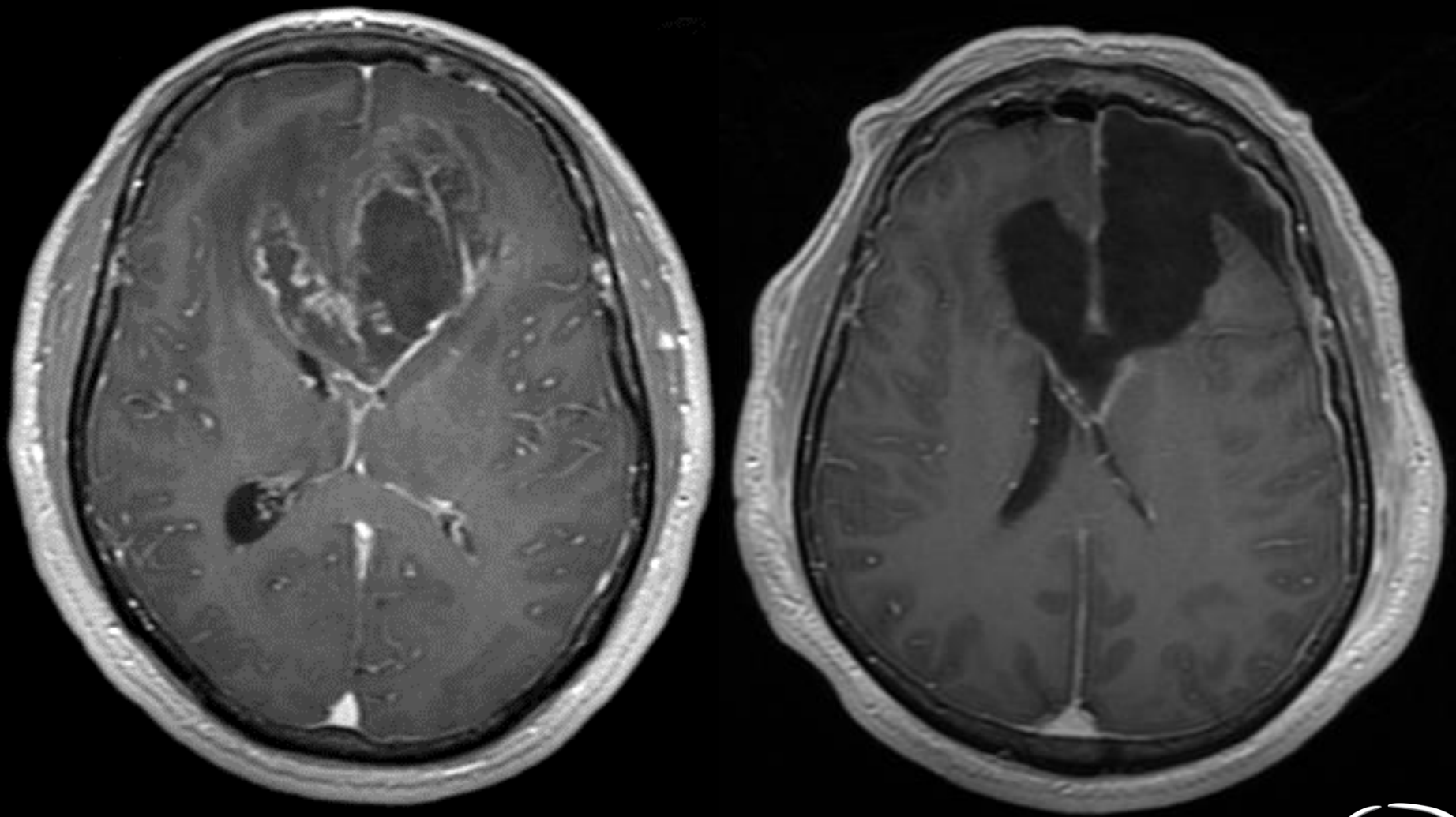
- **Cytoreduction impacts the rate for transformation**
  - ~~Non-insular LGGs: EOR > 90%: 5-year MPFS of 90% (p=0.09)~~ **EOR does not predict MPFS for pure oligodendrogliomas***
  - Insular LGGs: EOR > 90%: 5-year MPFS of 88% (p=0.04)*
- **Is the biological impact of EOR driven by hi**

Laura Snyder, MD
Assistant Professor of Neurosurge
Barrow Neurological Institute

*Smith *et al*. *J Clin Oncol*. 2008; 26(8):1338-45

*Snyder *et al*., *J Neurosurg*. 2014 120(2):309-14

High-Grade Gliomas: Extent of Resection



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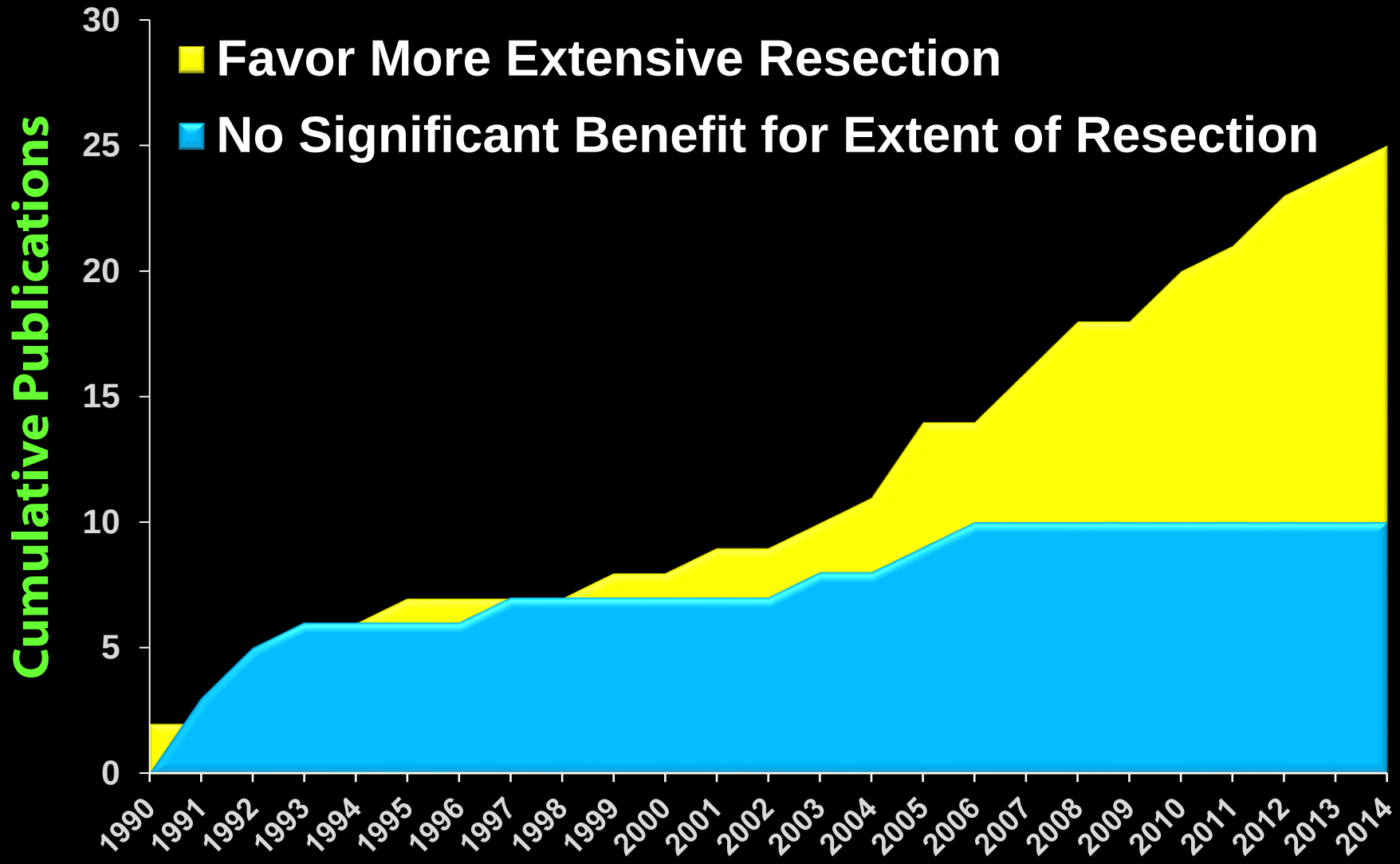
HGG Surgery in the Modern Literature



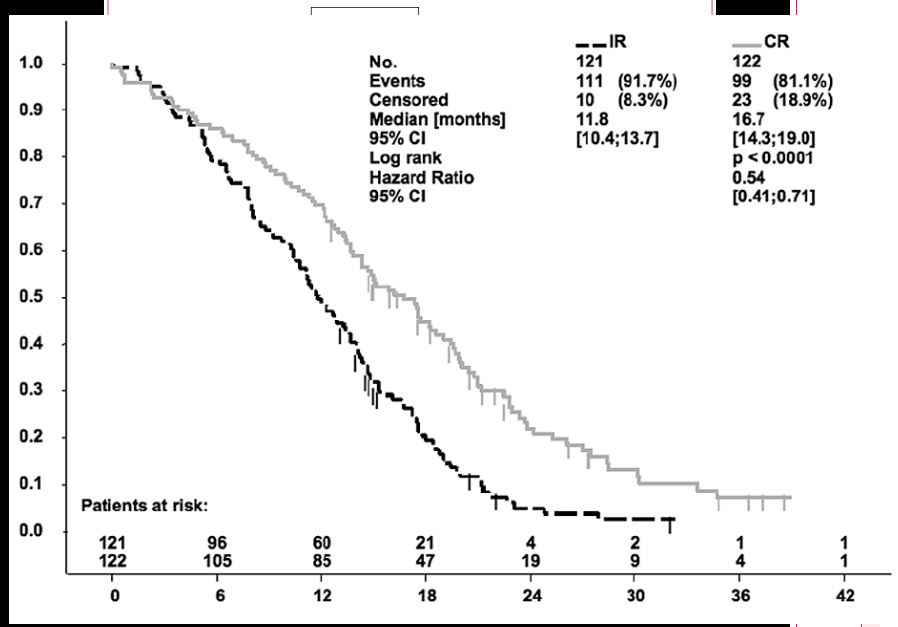
European 5-ALA Study Group

5-ALA Trial

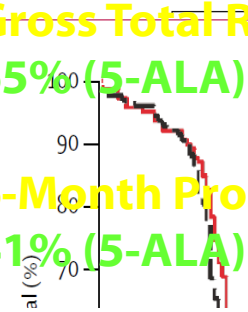
5-ALA Trial Restratification

Stummer *et al.*
Lancet Oncol, 2006

Stummer *et al.*
Neurosurgery, 2008



Gross Total Resection
65% (5-ALA)



6-Month Progression-Free Survival
41% (5-ALA)

Overall Survival
16.7 mo (5-ALA)

	5-aminolevulinic acid (n=136)	White light (n=131)	OR (95% CI)	p
patients	90 (65%)	47 (36%)	3·28 (1·99–5·40)	<0·0001*
e (years)	..	..	3·42 (2·06–5·70)†	<0·0001†
	..	..	..	0·679‡
·55	35/45 (78%)	20/43 (47%)	4·03 (1·60–10·14)	0·0025*
·55	55/94 (59%)	27/88 (31%)	3·19 (1·73–5·87)	0·0002*
nofsky performance scale	..	..	3·27 (1·98–5·40)†	0·0001†
	..	..	..	0·369‡
70–80	13/28 (46%)	9/31 (29%)	2·12 (0·72–6·20)	0·1676*
·80	77/111 (69%)	38/100 (38%)	3·70 (2·09–6·54)	<0·0001*
mour location	..	..	3·26 (1·97–5·40)†	<0·0001†
	..	..	..	0·351‡
Non-eloquent	45/65 (69%)	26/55 (47%)	2·51 (1·19–5·30)	0·0148*
Eloquent	45/74 (61%)	21/76 (28%)	4·06 (2·05–8·07)	<0·0001*

*Crude p value based on χ^2 test. †Common OR, adjusted for variable; p value based on Cochran-Mantel-Haenszel test. ‡Breslow-Day test for homogeneity of OR within variable.

Table 2: **Patients without residual tumour at early postoperative MRI: all patients, and stratified by age, performance status, and eloquent areas**

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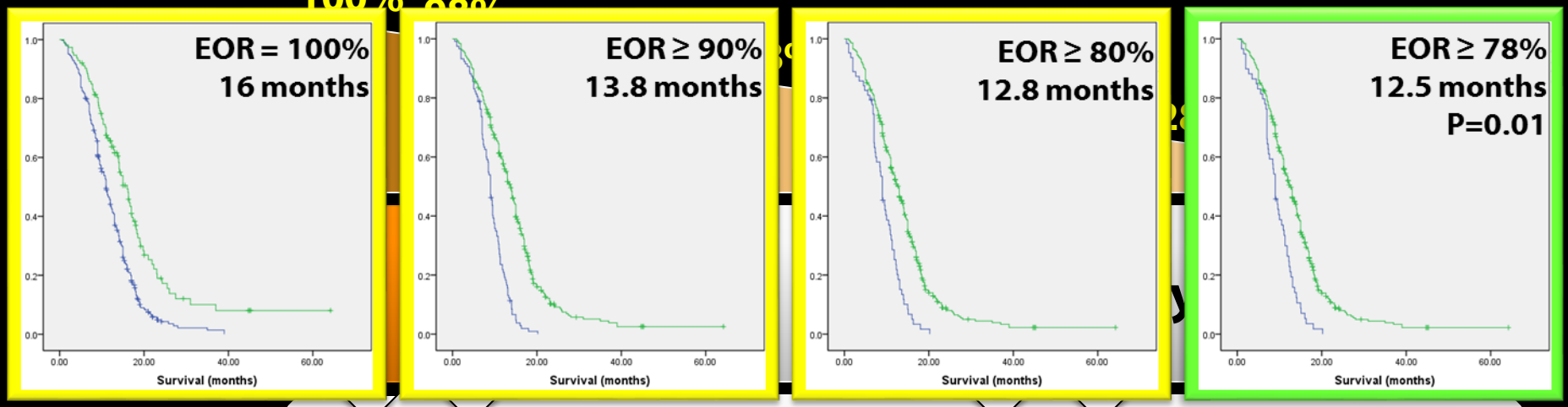
The Value of Extent of Resection: High-Grade Gliomas

New Management Paradigm for High-Grade Gliomas

500 Newly-Diagnosed Glioblastoma Patients



Survival benefit seen with ≥ 78% extent of resection

Adjuvant Therapy

Radiation + Chemotherapy

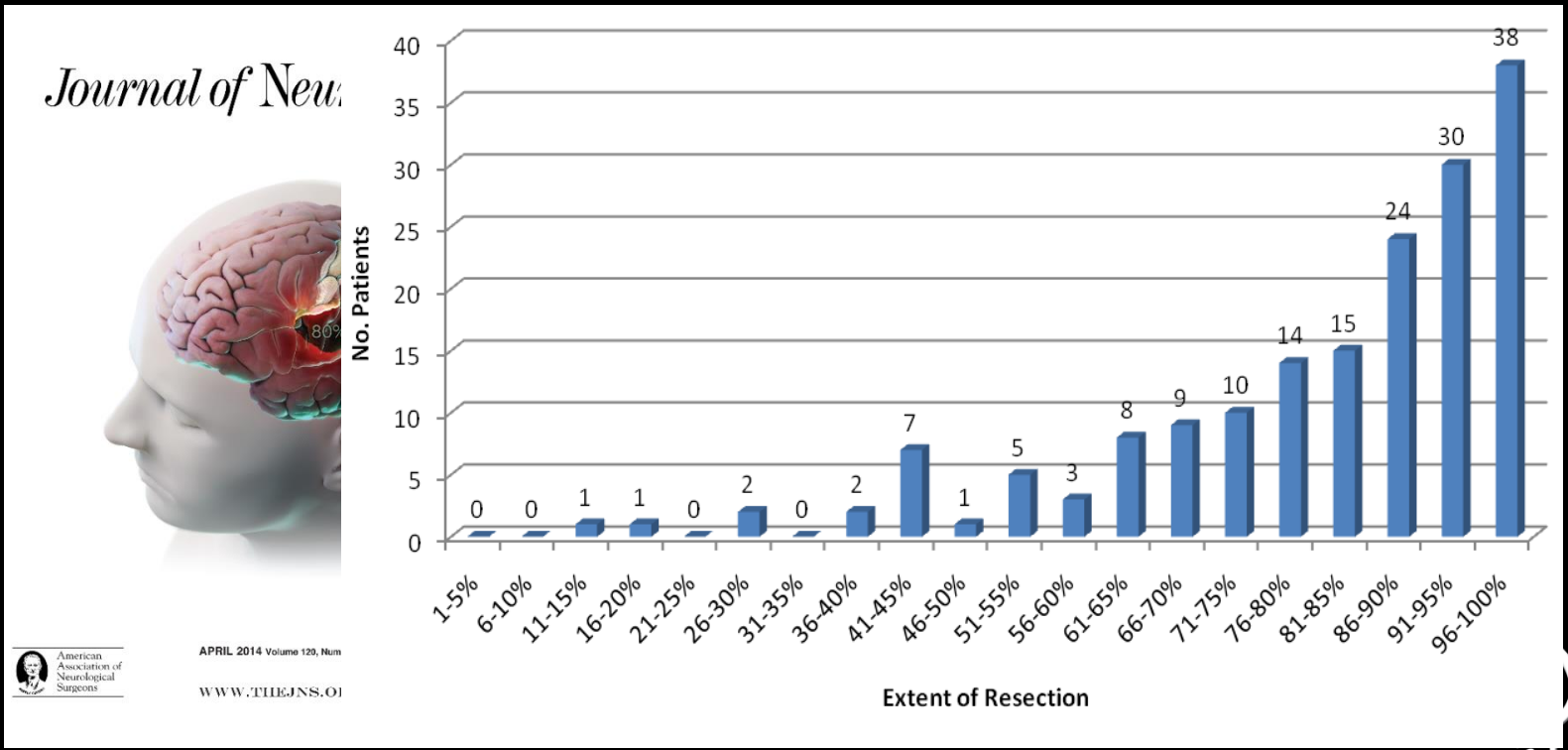
Sanai *et al.*, *J. Neurosurg.*, 2011 Jul;115(1):3-8

The Value of Extent of Resection: Recurrent High-Grade Gliomas

170 consecutive glioblastoma patients at first recurrence

- All had initial resection and Stupp regimen at first diagnosis
- All underwent repeat resection upon recurrence
- Mean clinical follow-up 22.6 months

Oppenlander *et al.*, *J. Neurosurg*. 2014 Apr;120(4):846-53



The Value of Extent of Resection: Recurrent High-Grade Gliomas

170 consecutive glioblastoma patients at first recurrence

- All had initial resection and temozolamide/RT at first diagnosis
- All underwent repeat resection upon recurrence
- Mean clinical follow-up 22.6 months

Oppenlander *et al., J. Neurosurg.* 2014 Apr;120(4):846-53

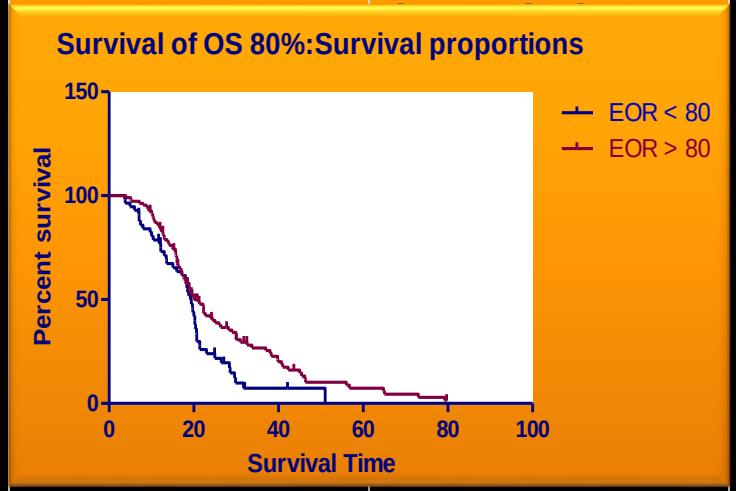
Graded Effect of Extent of Resection

Multivariate Cox Regression

Variable	P value
Age	0.0009
EOR	0.0018

Survival Benefit Seen Beyond 80%

EOR	Median OS

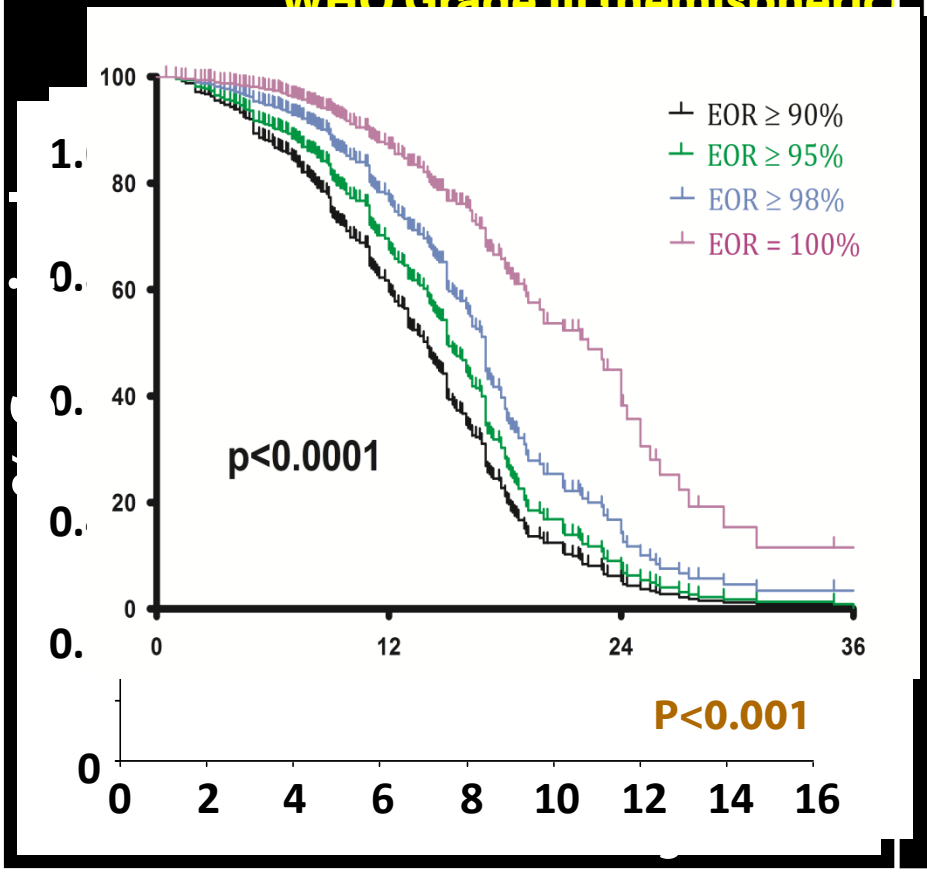


Is There Value to Extent of Resection?

Extent of resection improves glioma survival in a graded fashion

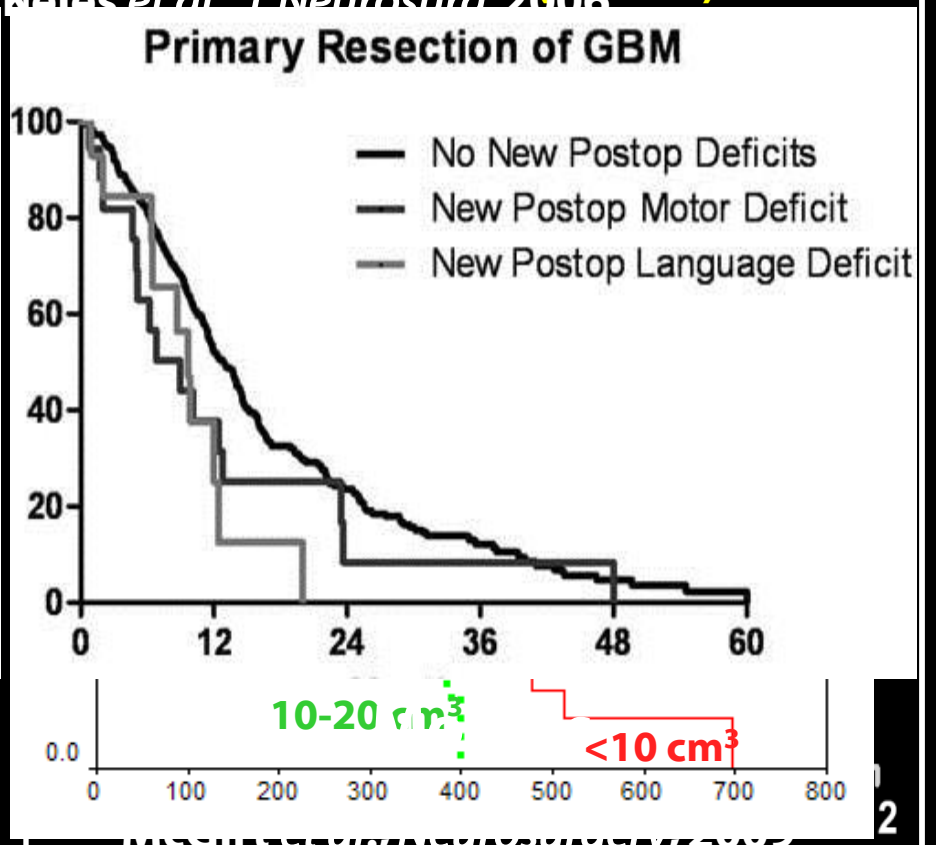
WHO Grade IV (glioblastoma)

Less tumor = longer survival



Less morbidity = longer survival

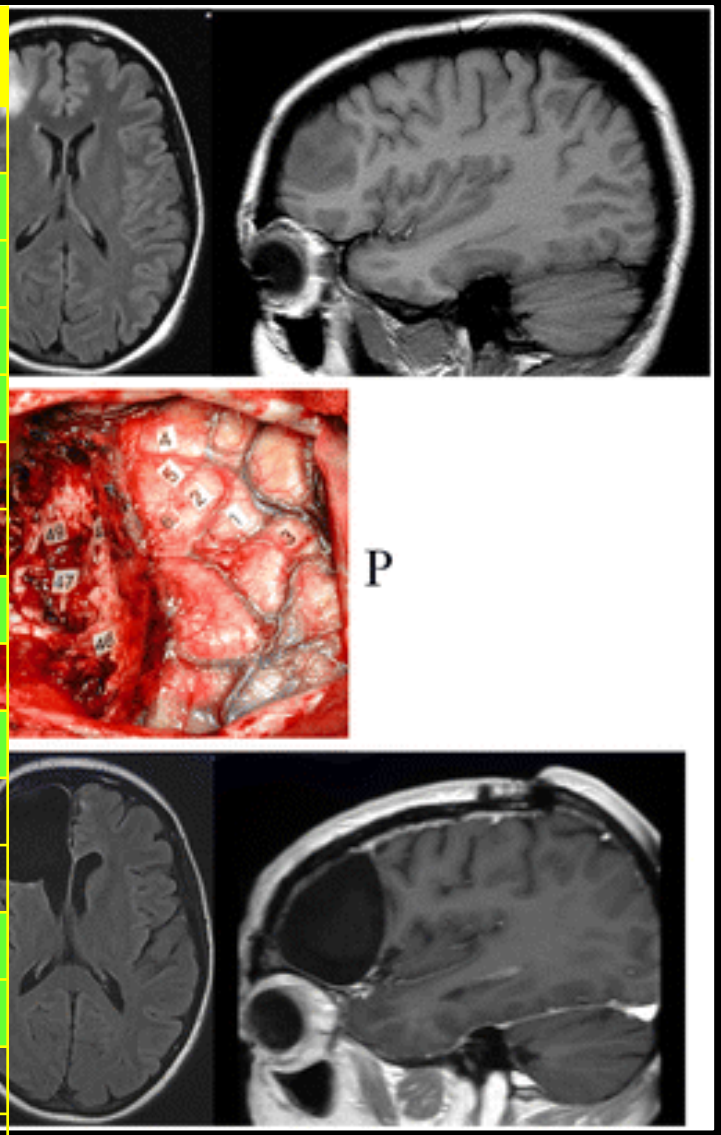
Keles *et al. J Neurosurg* 2006



McGirt et al./Neurosurgery/2009

Is There Value to Supramaximal Extent of Resection?

Age	Tumor Location	Tumor Grade/Type	Recurrence? (Years)
26	Frontal	Grade II Oligo	Yes (5.0)
38	Insular	Grade II Oligo	No (16.5)
31	Frontal	Grade II Oligo	No (13.0)
39	Parietal	Grade II Oligo	No (12.5)
45	Frontal	Grad	No (12.4)
32	Frontal	Grad	.1)
63	Insular	Grad	.8)
39	Frontal	Grad	No (10.9)
41	Frontal	Grad	.3)
48	Temporal	Grad	No (10.0)
35	Frontal	Grade II Oligo	Yes (2.7)
43	Frontal	Grade II Oligo	Yes (4.0)
59	Frontal	Grade II Oligo	No (8.4)
27	Temporal	Grade II Astro	No (8.2)
54	Insular	Grade II Oligo	Yes (6.7)
41	Frontal	Grade II Astro	Yes (7.5)



Duffau H, *Acta Neurochir (Wien)*, 2015 Nov 3

Glioma Rates of Gross-Total Resection: Results in the Modern Literature

2000-2010

High-Grade Glioma

Reported Rates of Gross-Total Resection

33% - 76%

Disaggregated Dataset

1412 of 2266 Tumors = 62.3% GTR

Low-Grade Glioma

Reported Rates of Gross-Total Resection

14% - 46%

Disaggregated Dataset

399 of 1462 Tumors = 27.3% GTR

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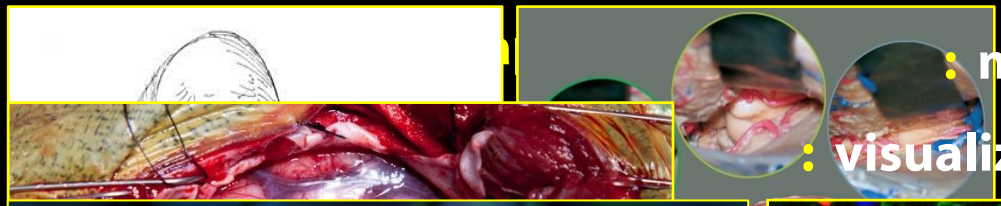
Maximizing Glioma Extent of Resection

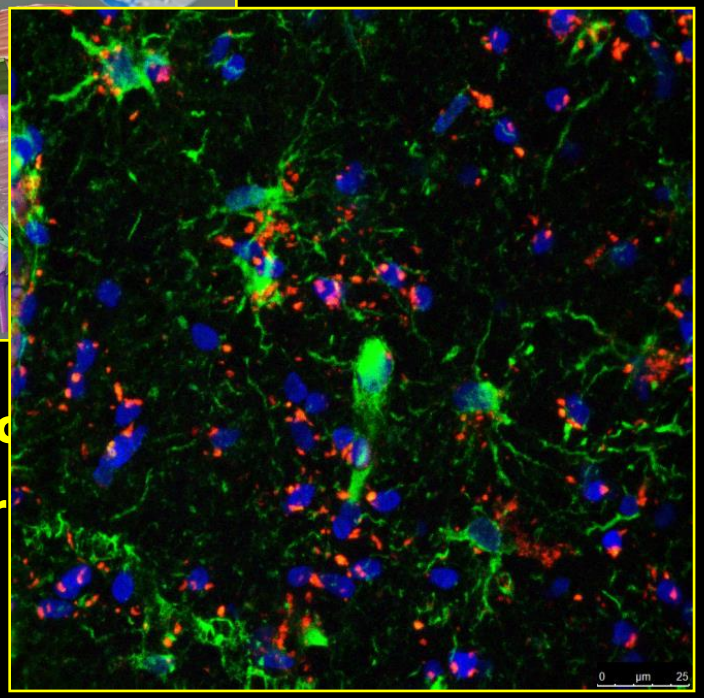
Fundamental Techniques

- **Operative Corridor Selection:** using gravity & arachnoidal planes



: minimizing morbidity

: visualizing cellular infiltration



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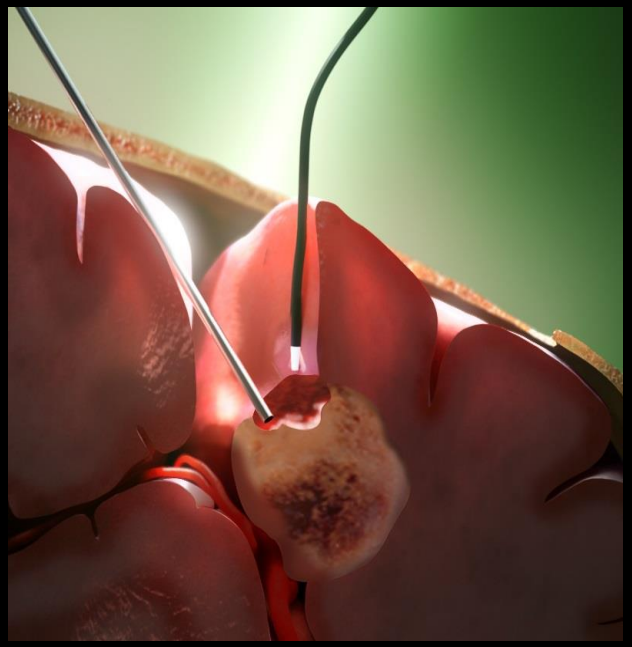
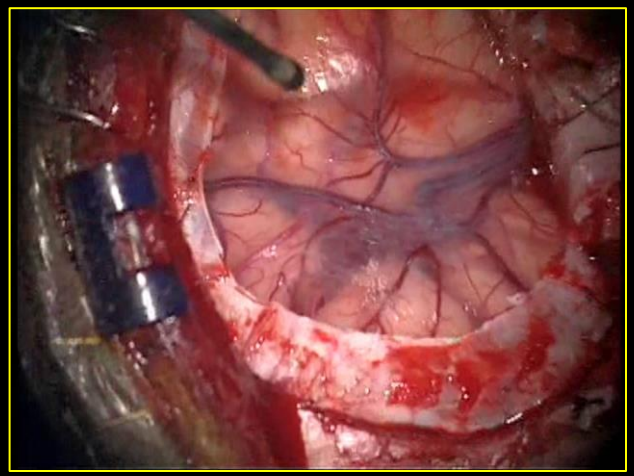
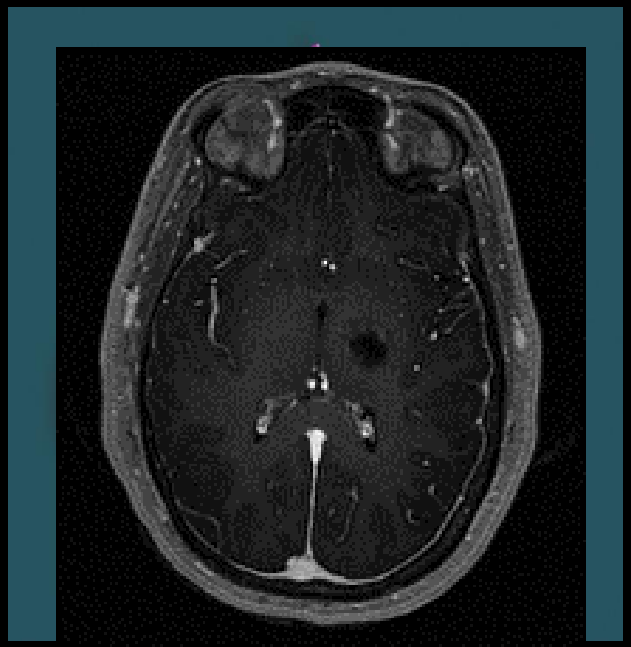
Maximizing EOR: Optimizing Exposure

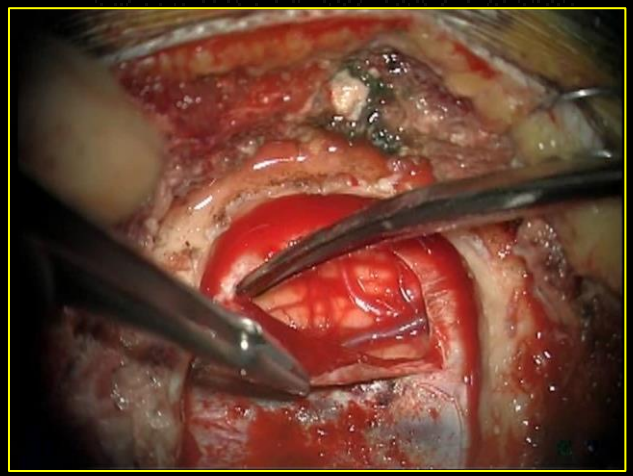
Arachnoidal Dissection



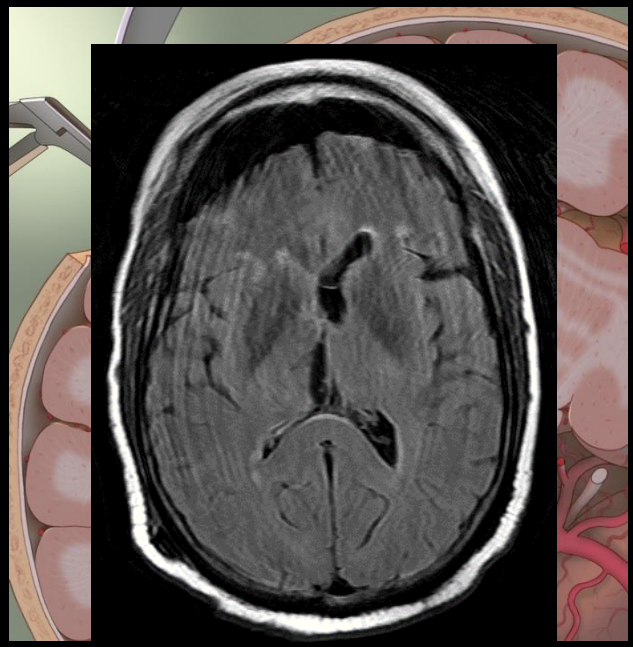


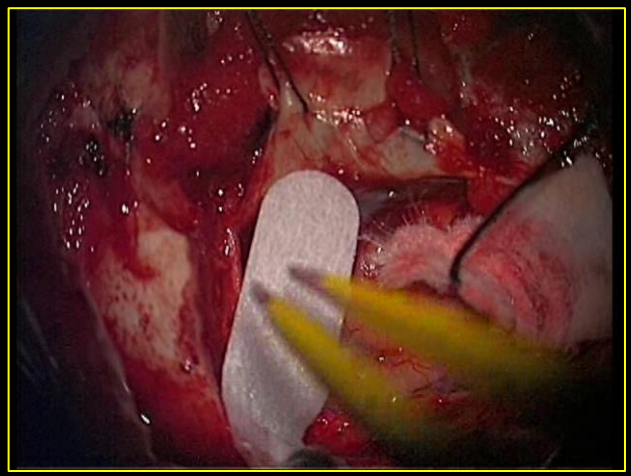
Entry-Point Selection





Gravity-Retraction



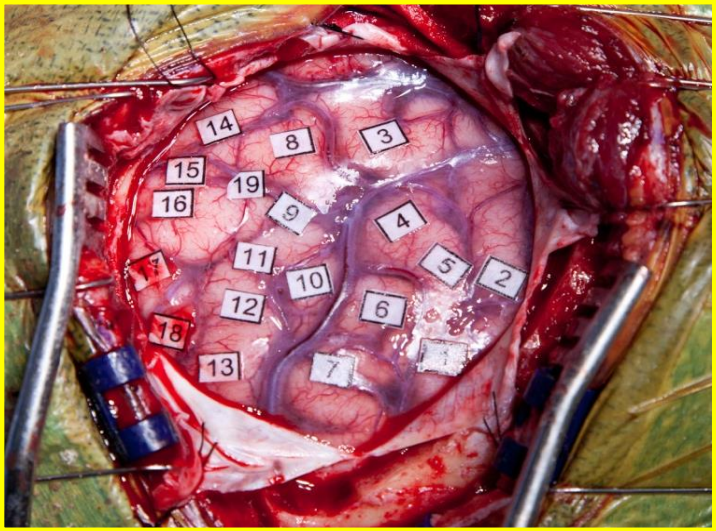


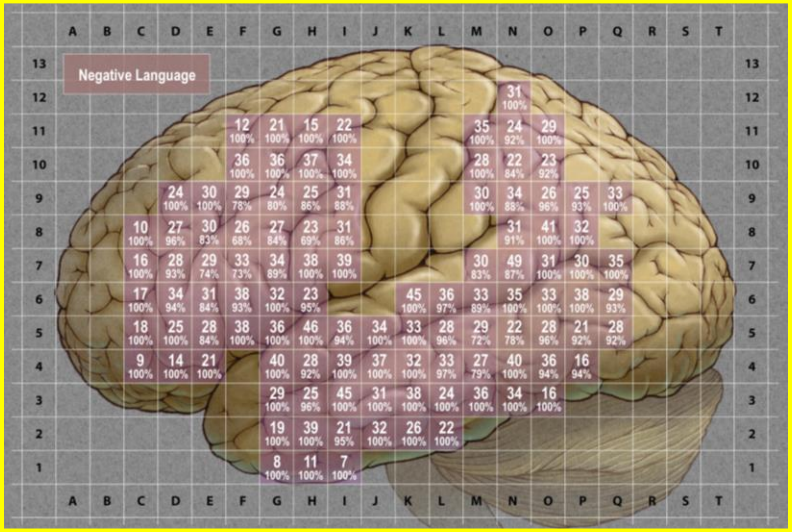
Maximizing Glioma Extent of Resection

Fundamental Techniques

✓ **Operative Corridor Selection**

❑ **Intraoperative Mapping Techniques: minimizing morbidity**





❑ **Fluorescence-Guided Surgery**

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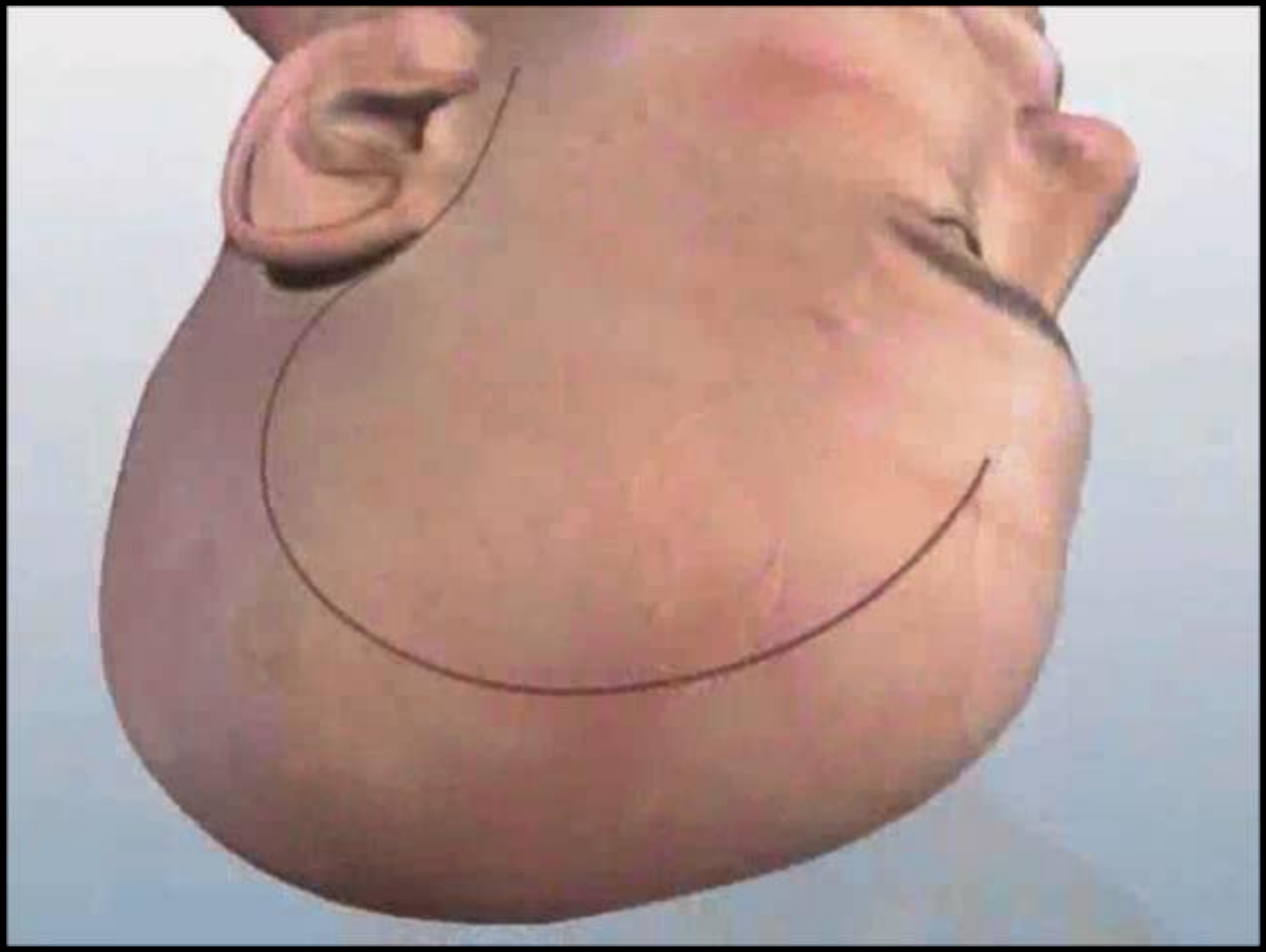
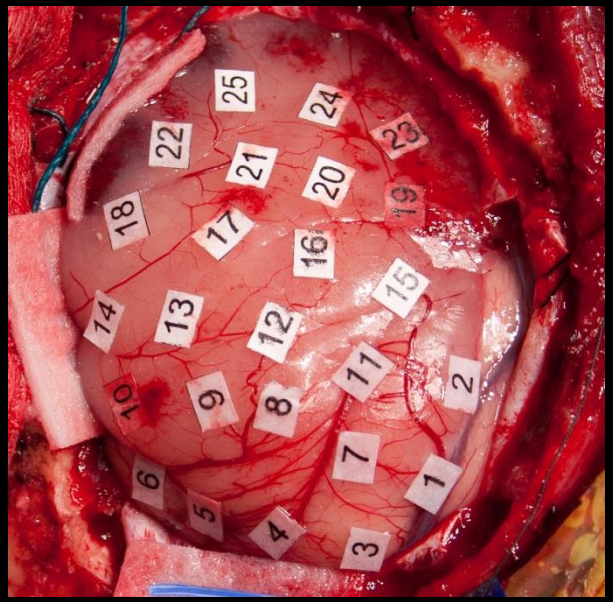
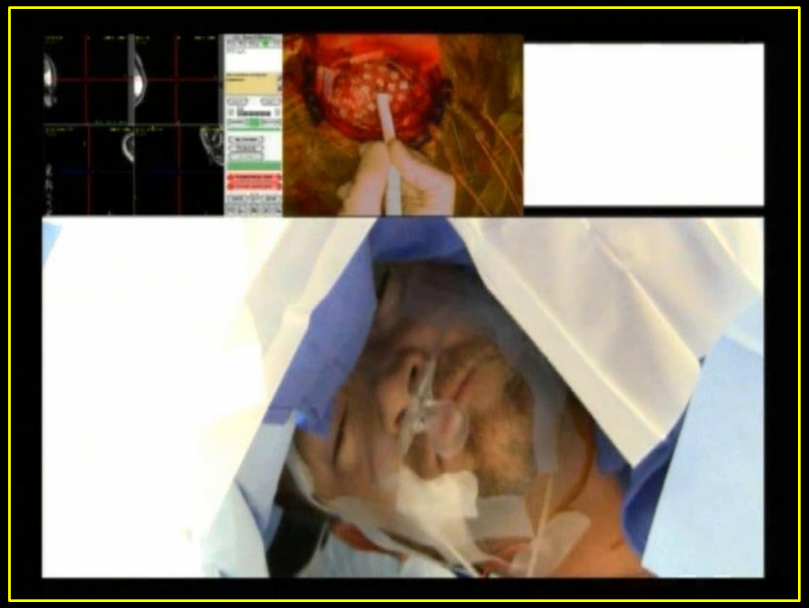
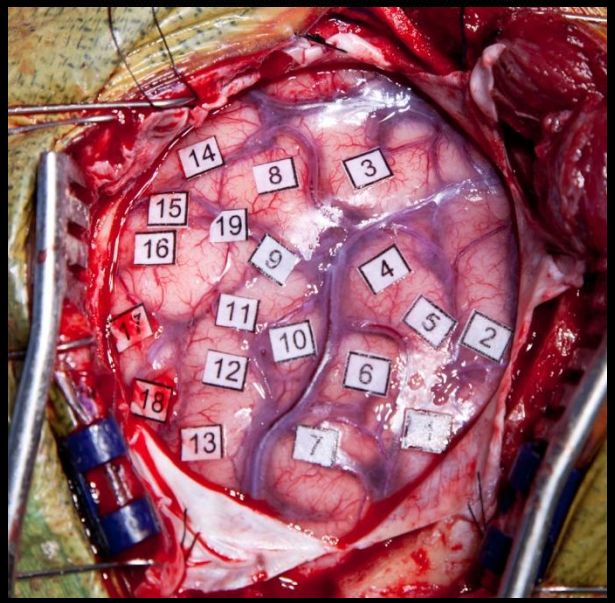
Intraoperative Stimulation Mapping:
Resect to the Boundaries of Function



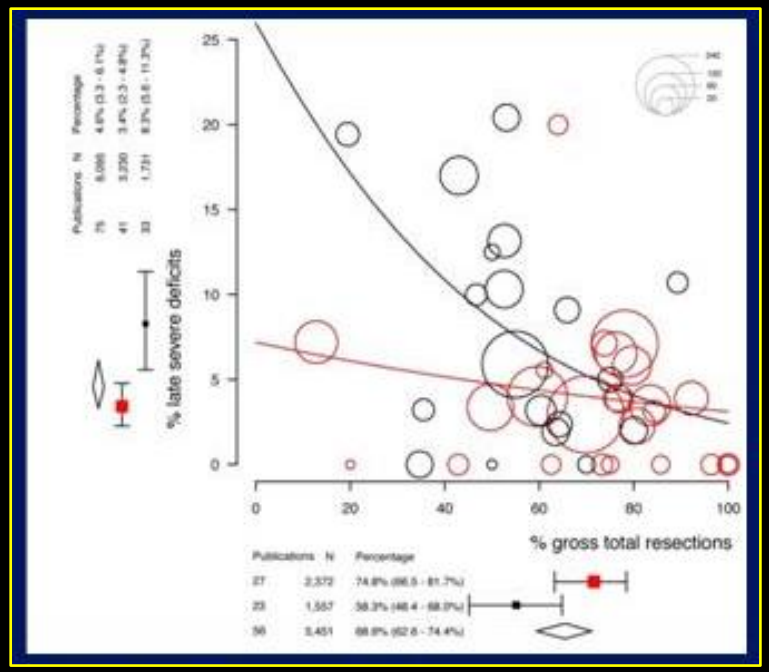
Maximizing EOR: Intraoperative Mapping

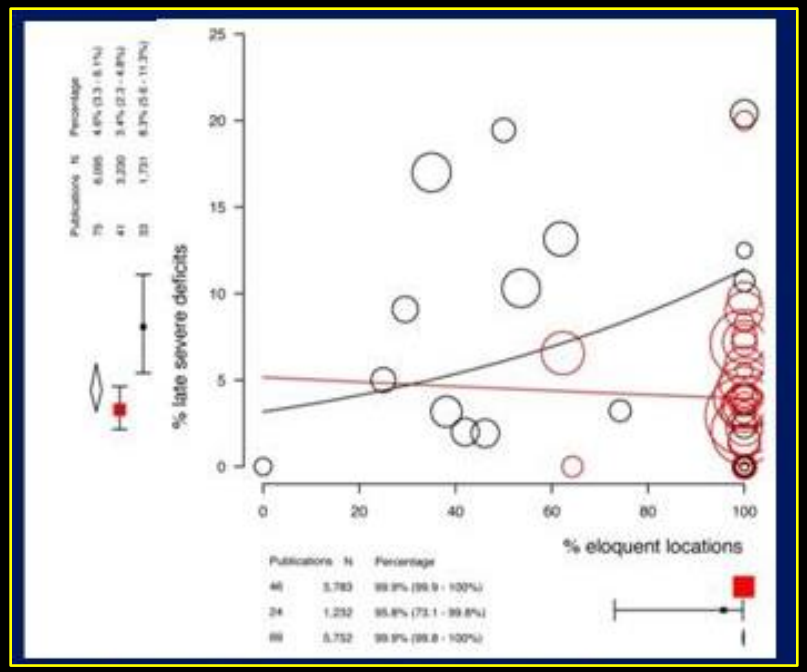






Maximizing EOR: Intraoperative Mapping





with stimulation mapping
without stimulation mapping

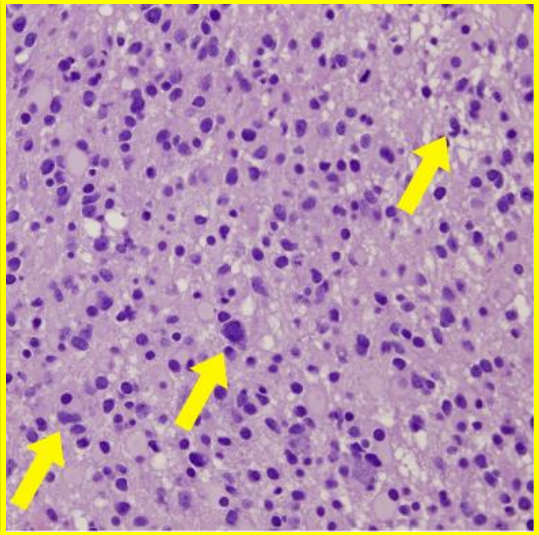
- Meta-analysis of 6095 low- and high-grade glioma cases
- Stimulation mapping improved gross-total resection in eloquent areas
- Two-fold reduction in late severe deficits with stimulation mapping (8.3% vs. 3.4%)

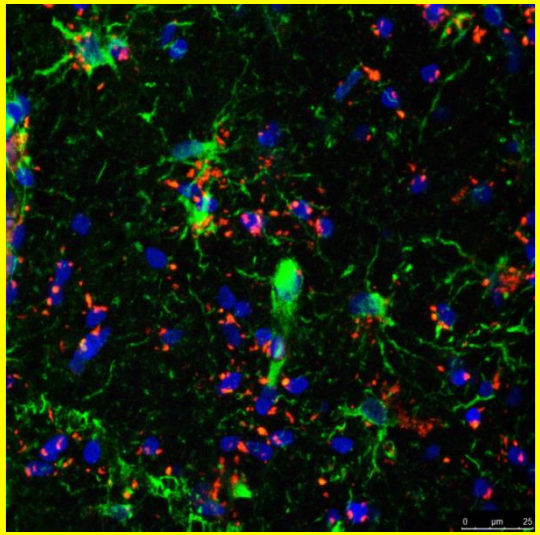
DeWitt *et al.*, *J Clin Oncol.* 2012 Jul 10;30(20):2559-65

Maximizing Glioma Extent of Resection

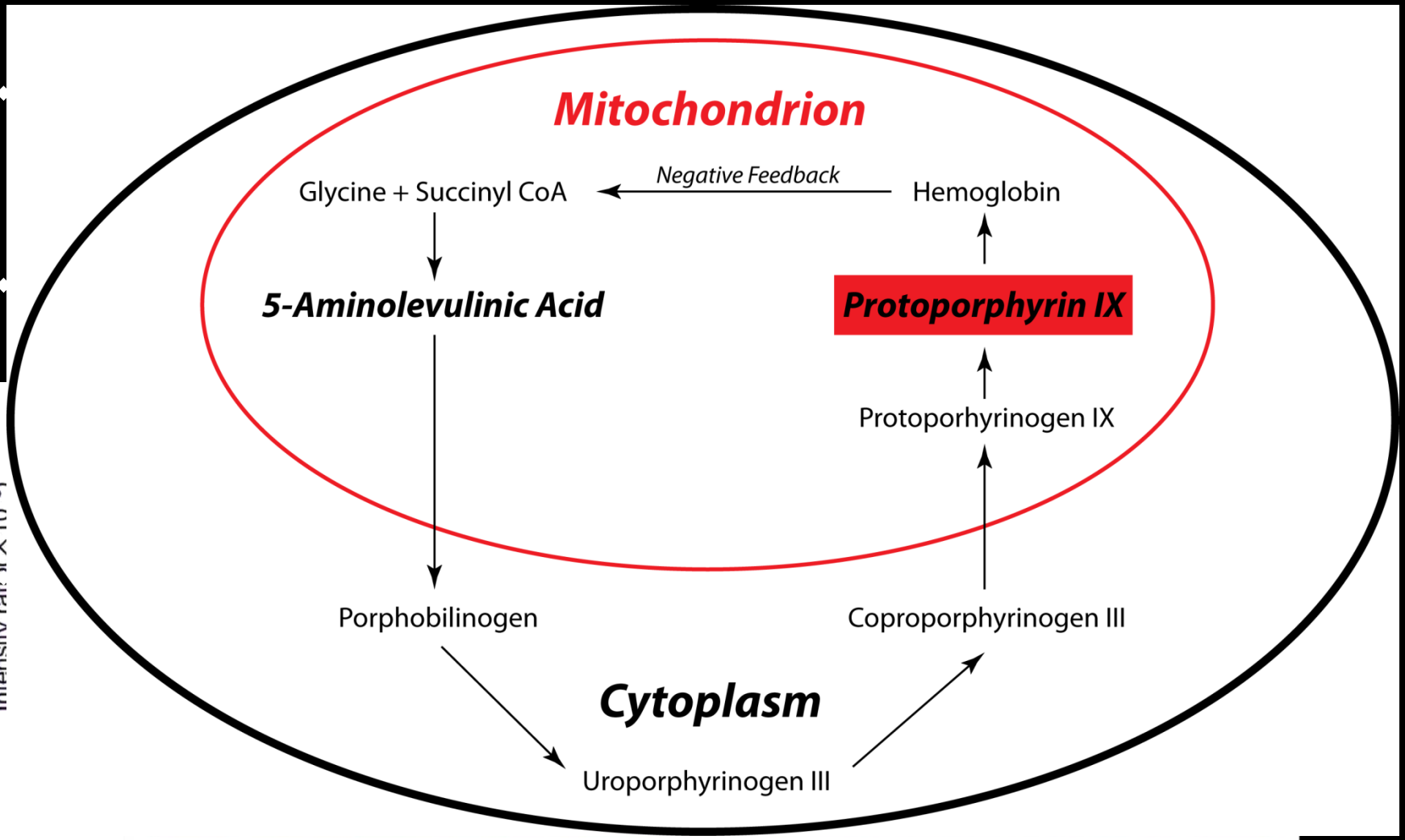
Fundamental Techniques

- ✓ **Operative Corridor Selection**
- ✓ **Intraoperative Mapping Techniques**
- ❑ **Fluorescence-Guided Surgery: visualizing cellular infiltration**





5-Aminolevulinic Acid (5-ALA)



Isihara *et al., Neurol Med Chir (Tokyo) 2007*

White Light

5-ALA HGG Fluorescence

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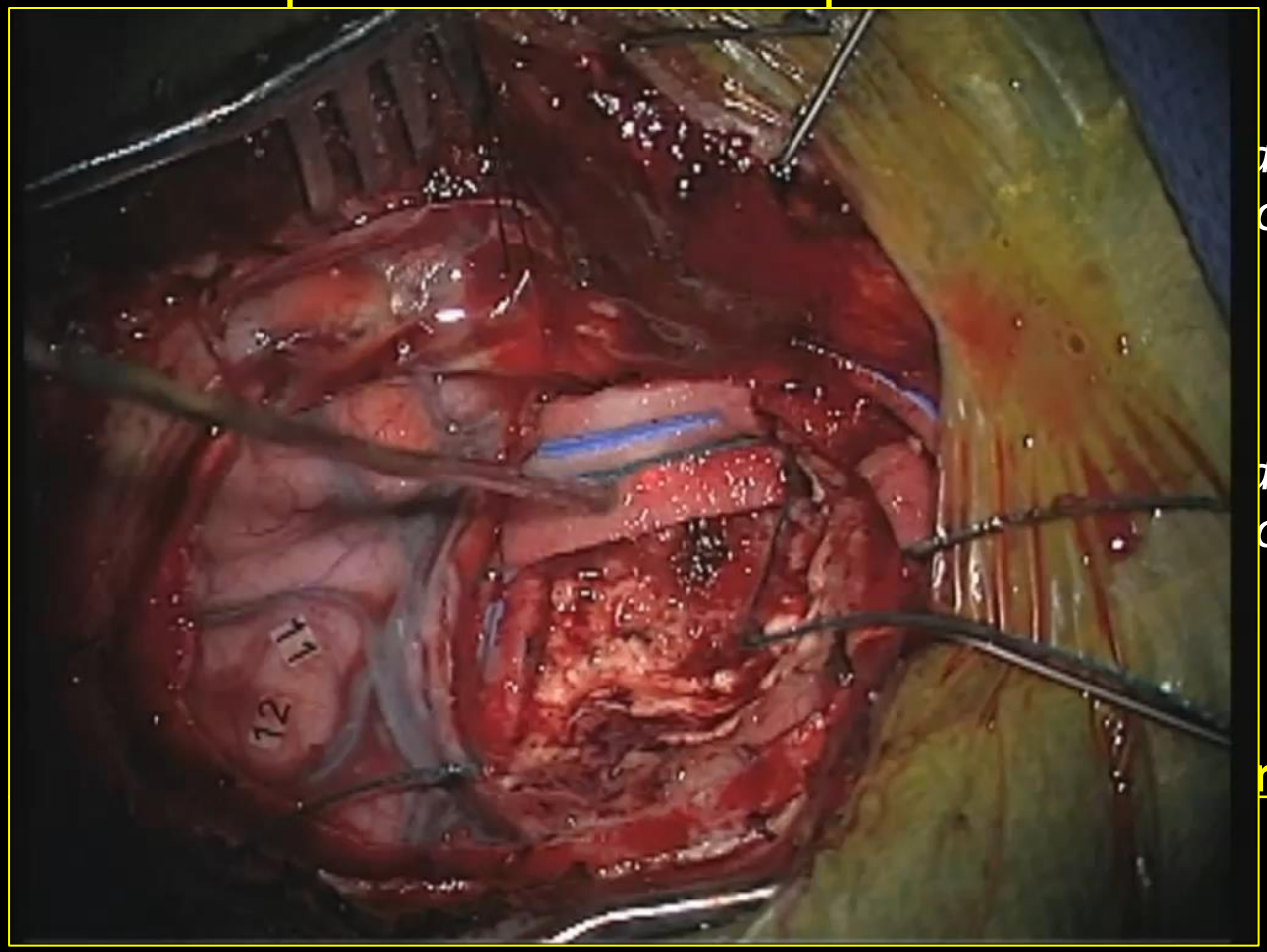
5-ALA: High-Grade Glioma Visualization



- Necrotic Center

  No Fluorescence

dual ***will enhance***

ostoperative MRI

- Border of Necrosis

  Deep Red

dual ***will not enhance***

ostoperative MRI

- Marginal Tissue

  Lighter Pink

m for high-grade gliomas

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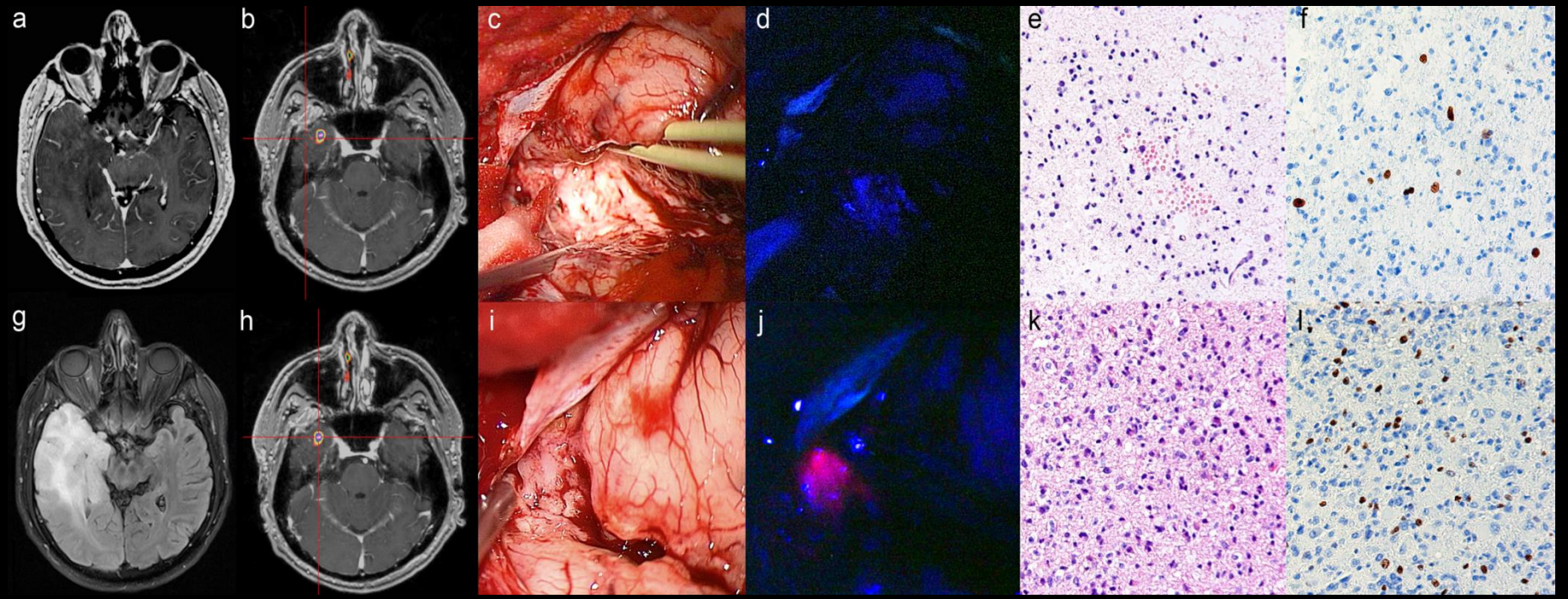
Roberts *et al.*, *J Neurosurg.* 2011 Mar;114(3):595-603

5-ALA in Non-Enhancing Gliomas

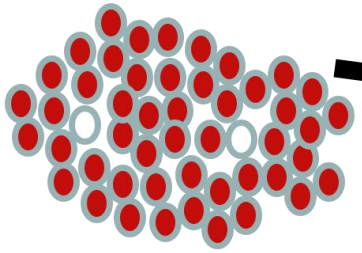
- Focal PpIX fluorescence observed in **46% of nonenhancing gliomas**
- **85%** of PpIX(+) nonenhancing gliomas had WHO grade III histology
- **Proliferation index, cell density, and nuclear pleomorphism** were significantly higher in areas of focal PpIX fluorescence



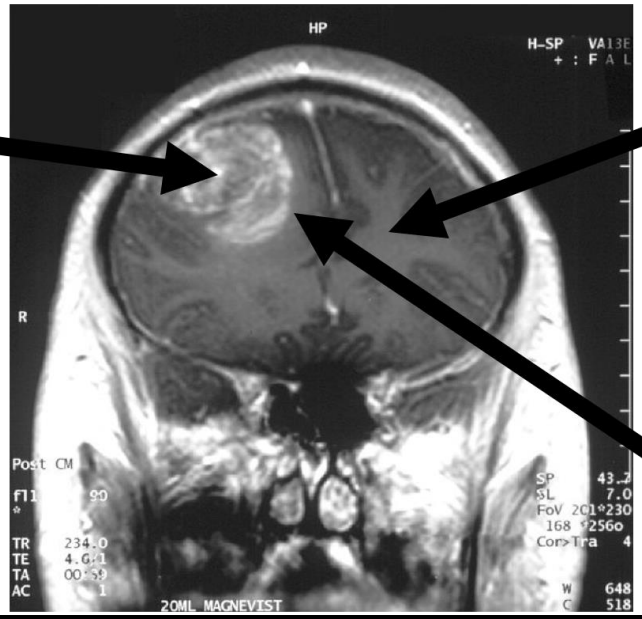
Widhalm *et al.*, *PLOS One 2013*; Oct 18

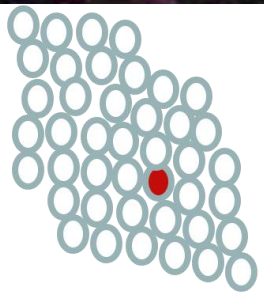
Limitations of Wide-Field Microscopy

- Image intensity of wide-field microscopy is subjective, particularly at the diffuse margins of a glioma
- P[illegible]t[illegible]ations

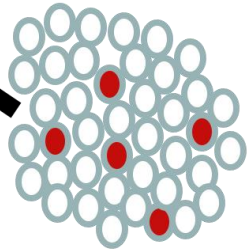


> 90% tumor cells





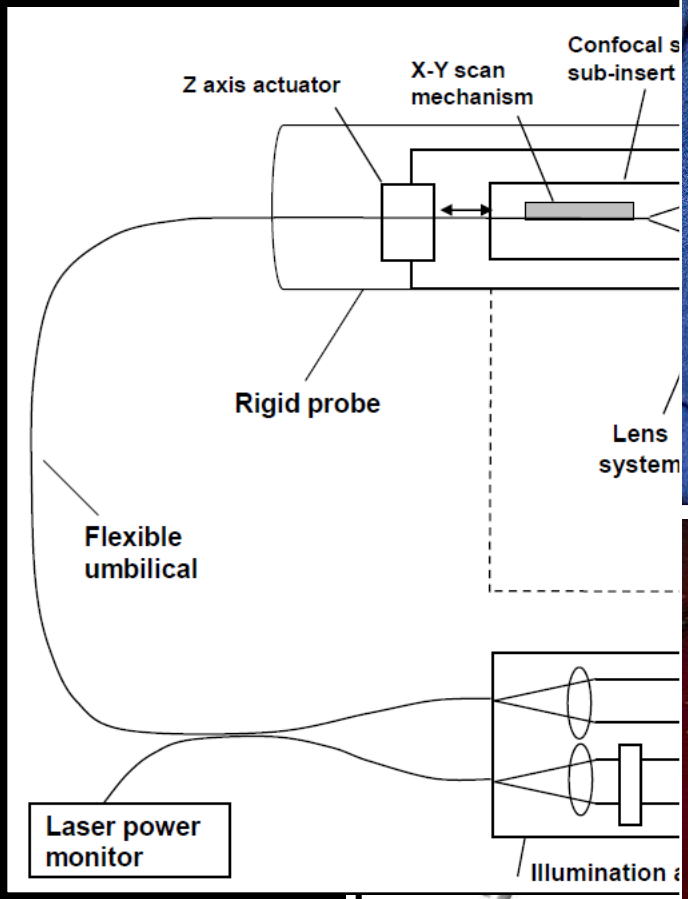
< 1% tumor cells

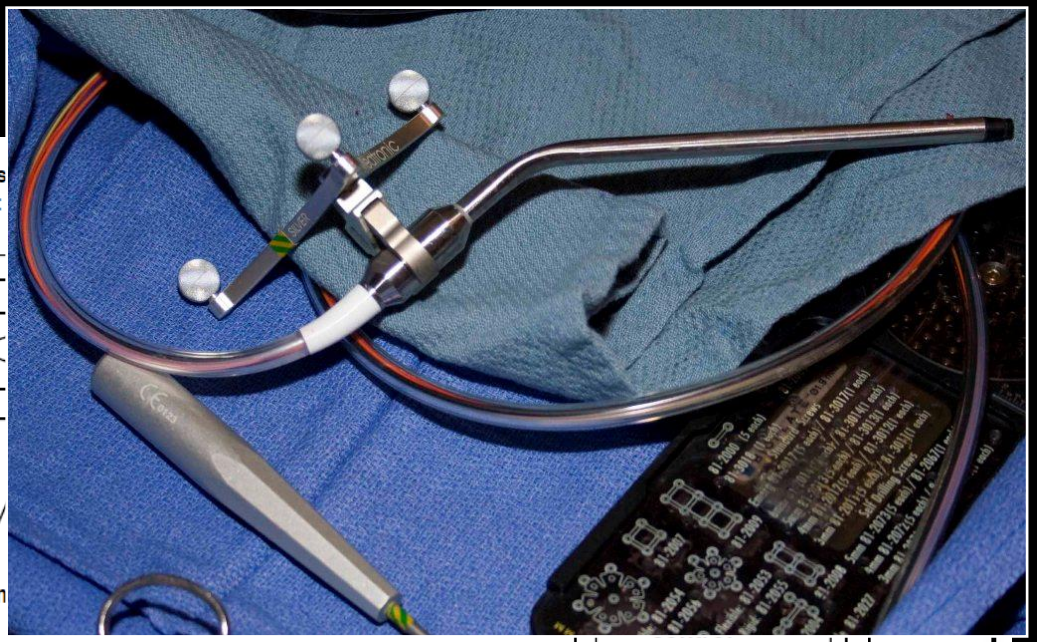


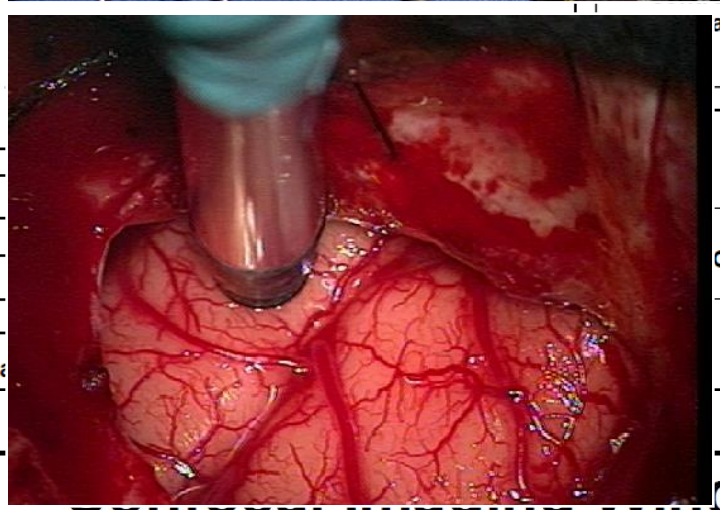
5 - 50% tumor cells

Liu JT *et al.*, *Neurosurgery* 2014 Jul;75(1): 61-71

Intraoperative Confocal Microscopy:
Cellular Resolution







BALANCE Trial: Low-Grade Gliomas

All Gliomas

High Expected EOR

Low Expected EOR

BARROW
ALA
INTRAOPERATIVE
CONFOCAL
EVALUATION

h C

hancing Glioma

Intraoperative Fluorescence

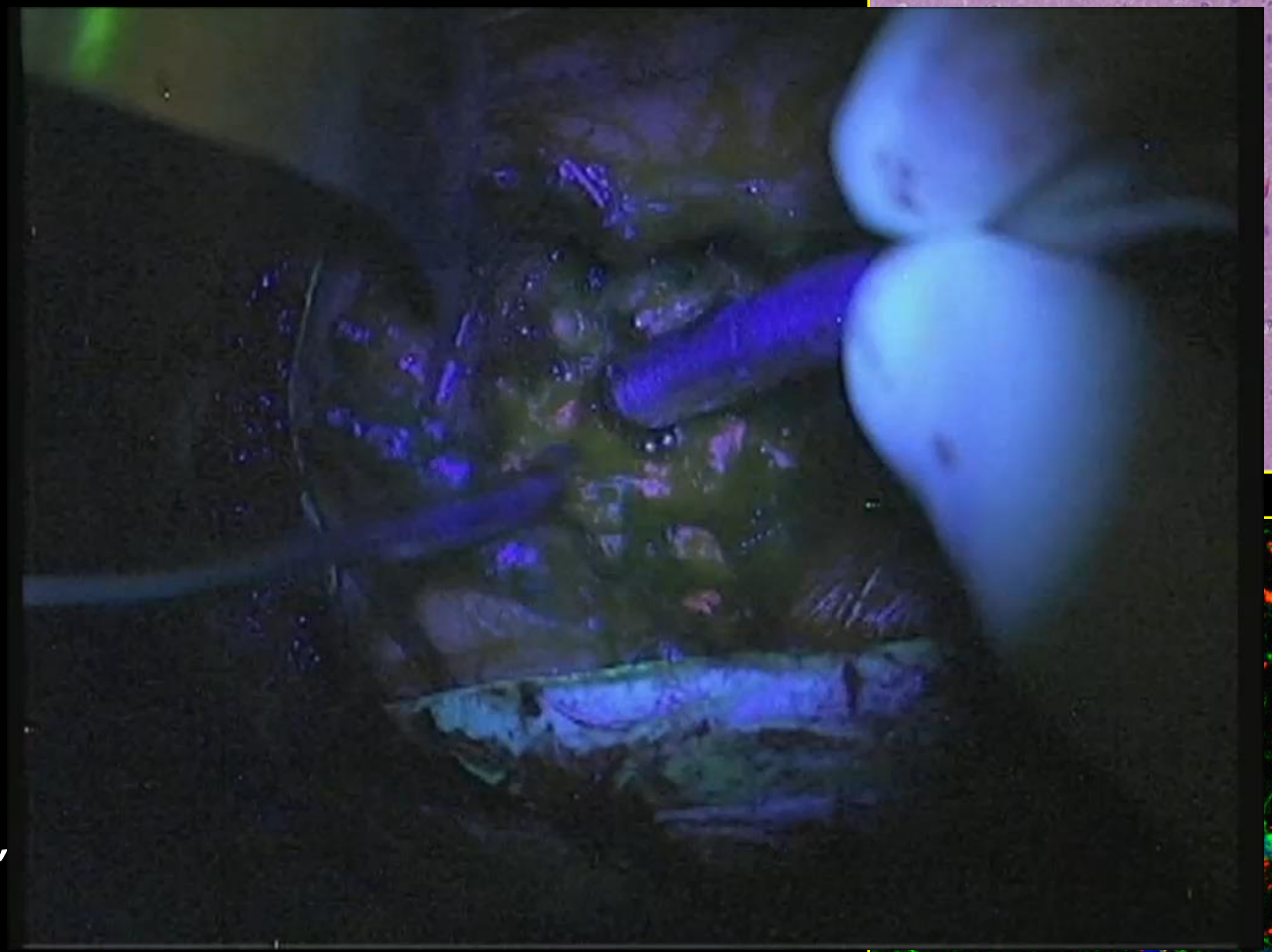
Intraoperative Fluorescence

+

Intraoperative Confocal

PI: Nader Sanai / NCT01502280

5-ALA Visualization of Low-Grade Gliomas



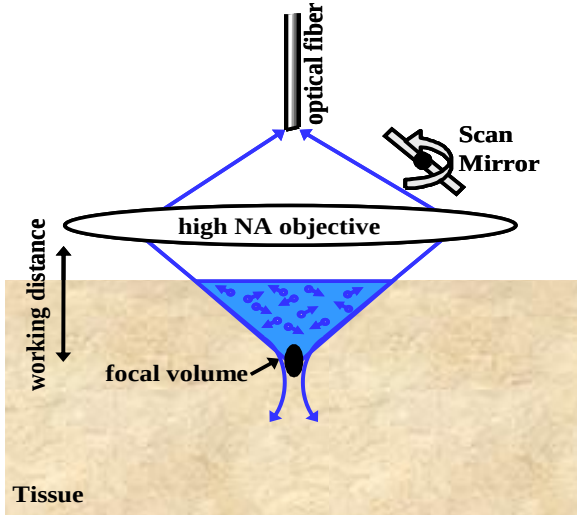
Sanai *et al.*,

5-ALA Visualization of Low-Grade Gliomas

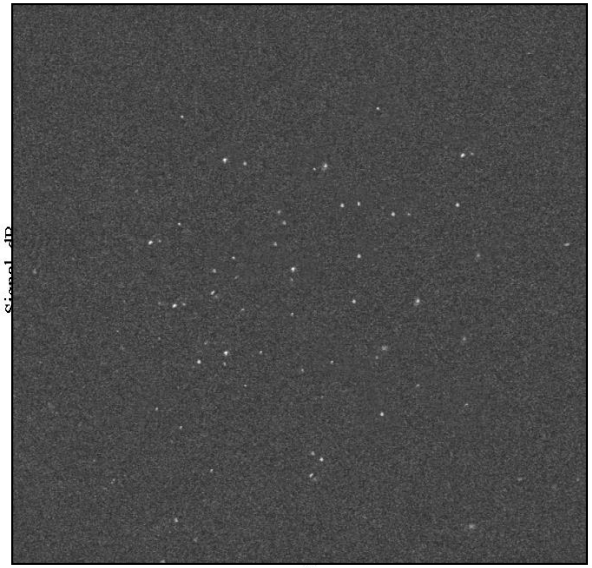
					Microscopic Fluorescence			
Age	*Sex*	*Tumor Location*	*Tumor Grade*	*Macroscopic Fluorescence*	*Initial Encounter*	*Mid-point Resection*	*Cavity Margin*	*Volumetric EOR*
19	M	Frontal	Grade I	No	Yes	Yes	Yes	100%
37	F	Frontal	Grade II/III	No	Yes	Yes	Yes	100%
21	M	Frontal	Grade II	No	Yes	Yes	No	98%
64	M	Temporal	Grade II	No	Yes	Yes	No	87%
39	F	Parietal	Grade II	No	Yes	Yes	Yes	99%
32	F	Frontal	Grade II	No	Yes	Yes	No	94%
38	F	Temporal	Grade II	No	Yes	Yes	Yes	92%
49	M	Insular	Grade II	No	Yes	Yes	Yes	93%
24	M	Temporal	Grade II	No	Yes	Yes	No	97%
30	M	Insular	Grade II	No	Yes	Yes	Yes	90%

Sanai *et al., J. Neurosurg*. 2011; 115(4): 740-8

Intraoperative Dual-Axis Confocal Microscopy



Single-Axis Confocal



Superior Optical Sectioning

- High axial resolution needs high-NA lens
  - ❖ Dual-Axis Confocal (DAC) architecture
- Short working distance improves rejection of out-of-focus light
- More background noise from scattered light

Enhanced Sensitivity & Contrast

- ❖ Light scattered along the illumination path (blue) is less likely to be collected

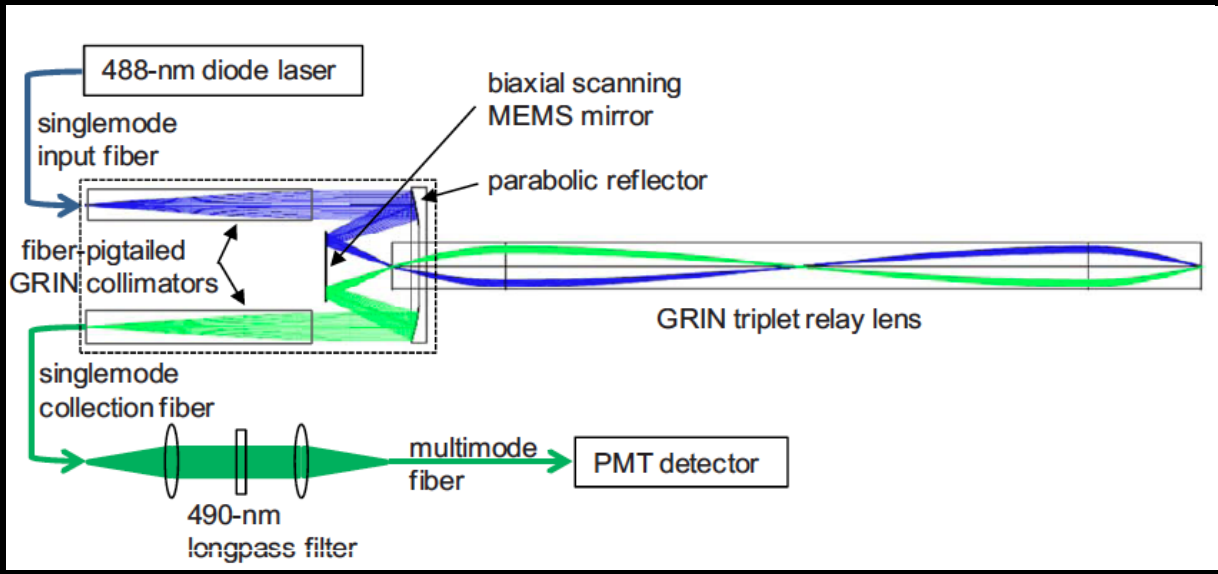
Improved Optical Clarity

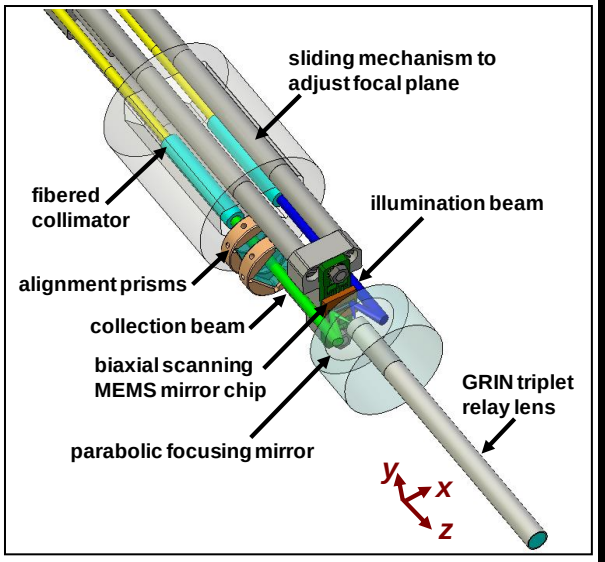
- Low numerical aperture (NA) lenses
  - ❖ Off-axis path traversed by photons
- Long working distance eliminates noise due to back reflections
- Less noise from scattered light

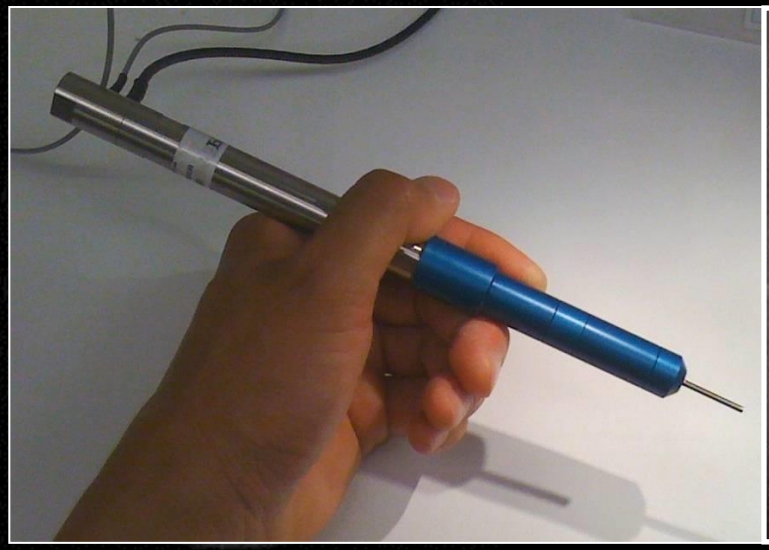
Liu *et al.*, *Neurosurgery* 2014

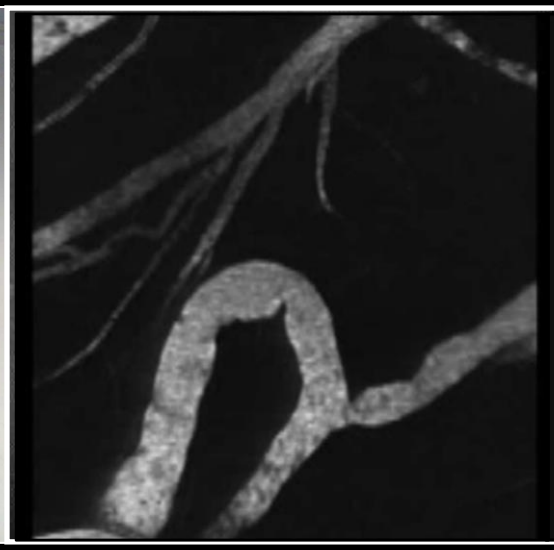
BARROW Neurological Institute

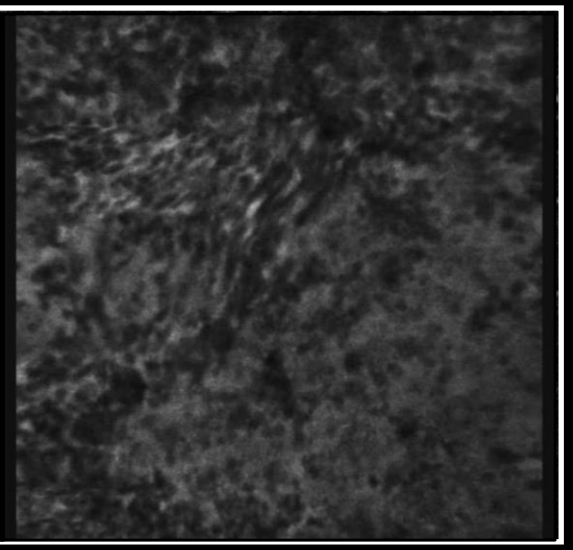
Intraoperative Dual-Axis Confocal Microscopy









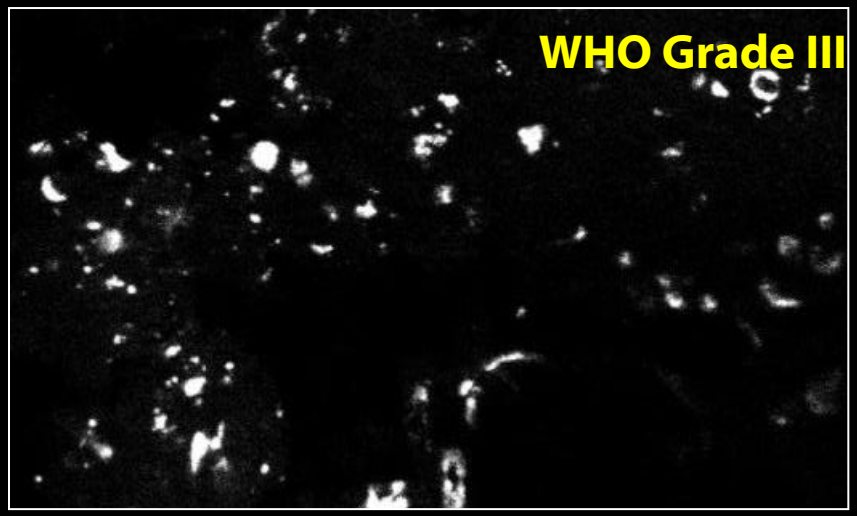


NCI 1R01CA175391 (PI: Sanai)

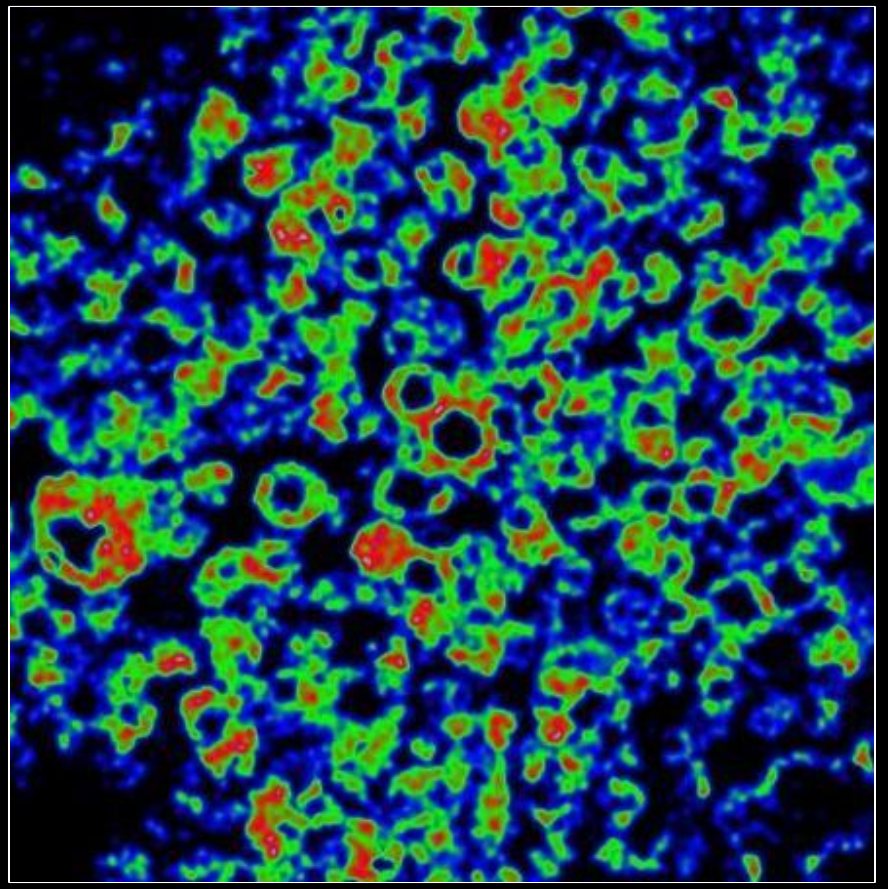
Normal Vasculature

Glioma Vasculature

Quantification of Microscopic Tumor Burden



PpIX(+) Human Glioma



Real-Time Cell Density Heat Map

Conclusions

- Extent of resection matters for all grades of gliomas
- Cytoreduction can delay malignant transformation and alter the natural history of low-grade gliomas
- 80% is the extent of resection threshold for newly-diagnosed and recurrent high-grade gliomas
- Intraoperative stimulation mapping is a critical to maximize extent of resection and minimize morbidity
- In the near future, extent of resection will be measured by microscopic tumor burden at the cavity margins

Thank you for your attention

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