



**5th Annual
Brain Metastases
Research and
Emerging
Therapy
Conference**

October 2-3 2015
Marseille, France

The value of 5-ALA induced fluorescence for resection of Brain Metastases

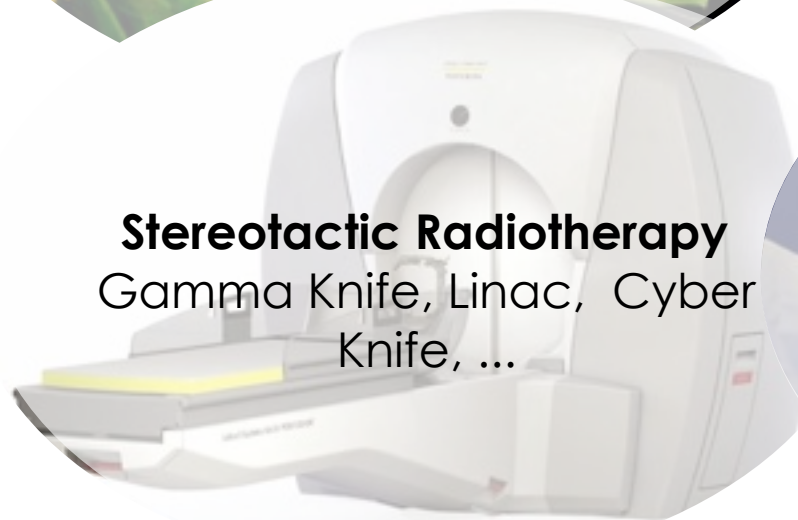
Georg Widhalm



MEDICAL
UNIVERSITY
OF VIENNA

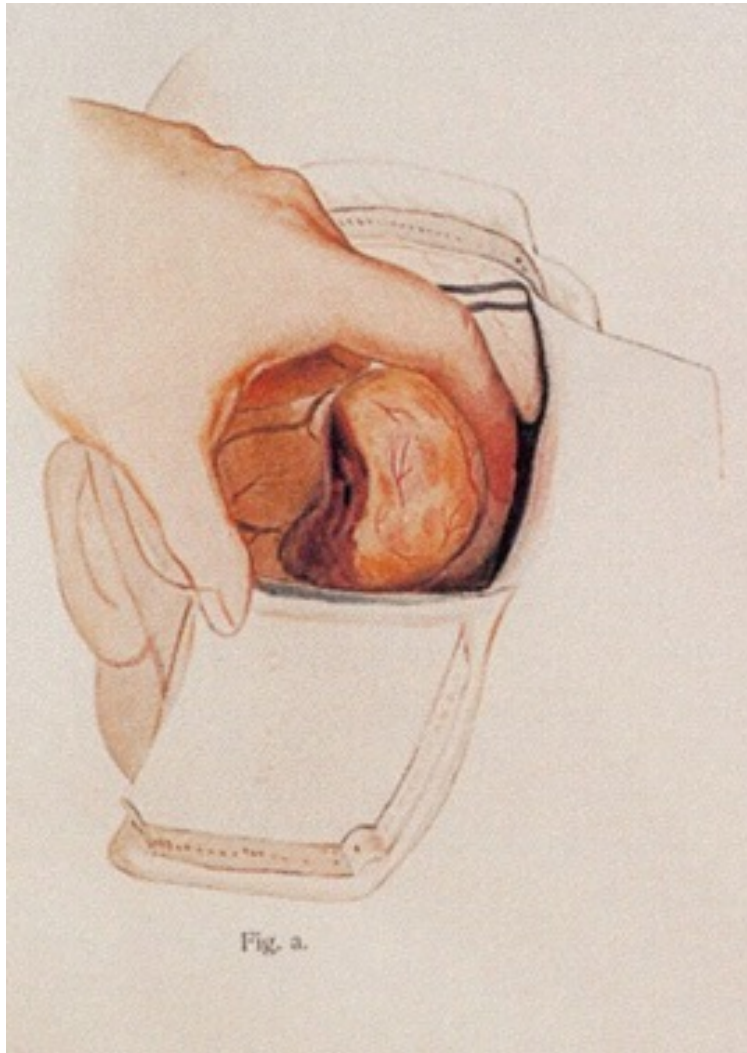


Treatment options for BM



Neurosurgical Resection

In the past



Fedor Krause
1857 - 1937

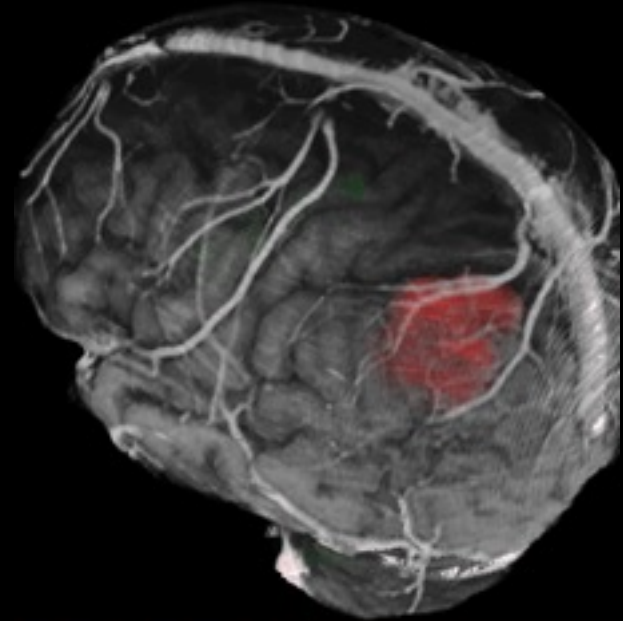
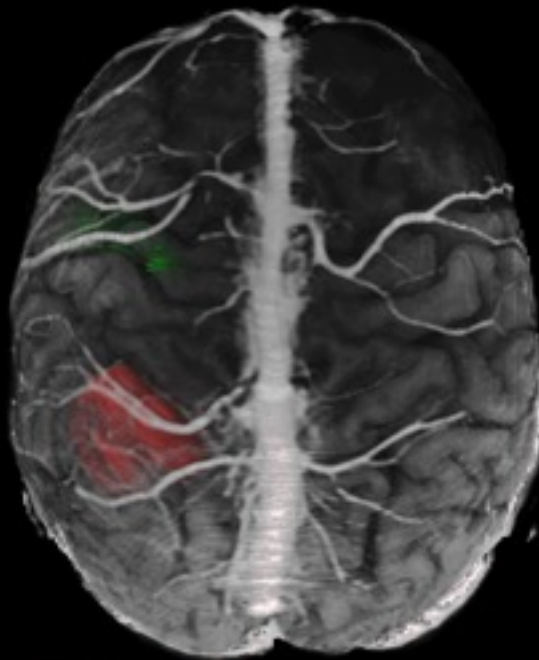
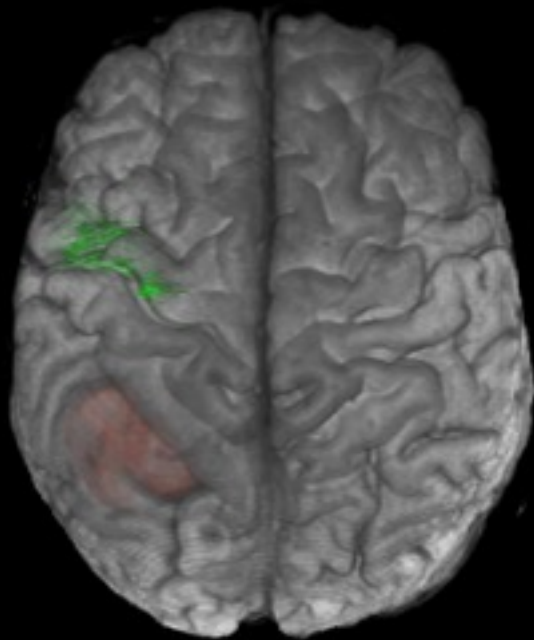
Fedor Krause.

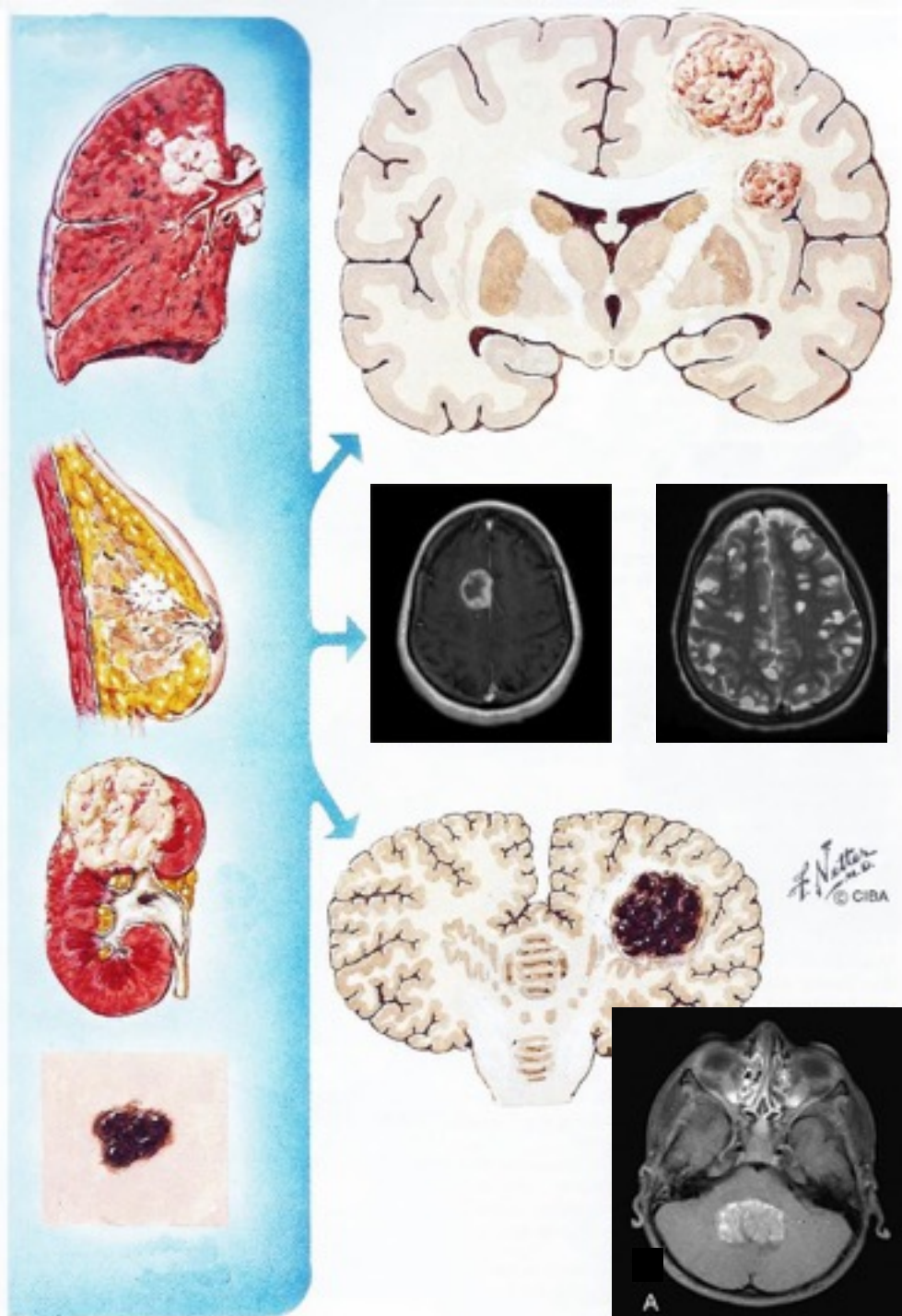
Neurosurgical Resection In 2015



Magnetic Resonance Imaging (MRI)

Preoperative planning

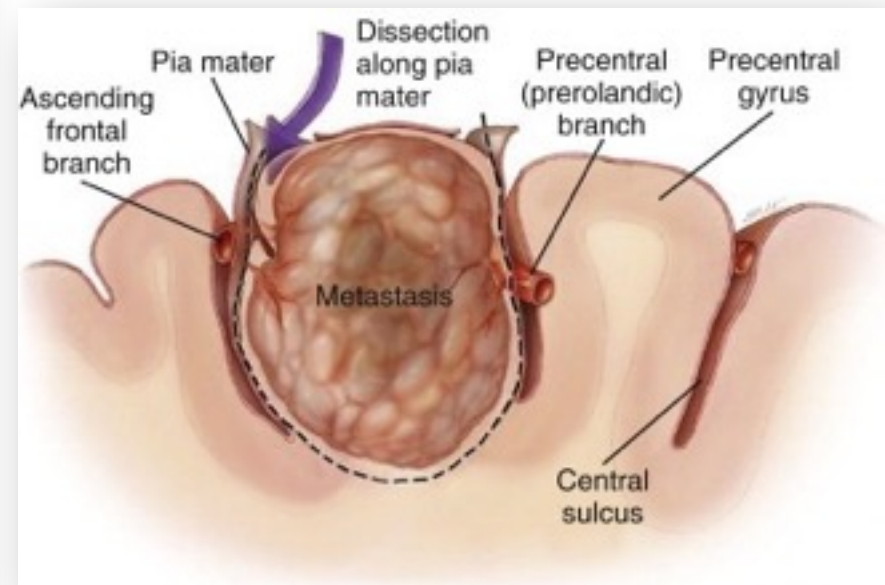
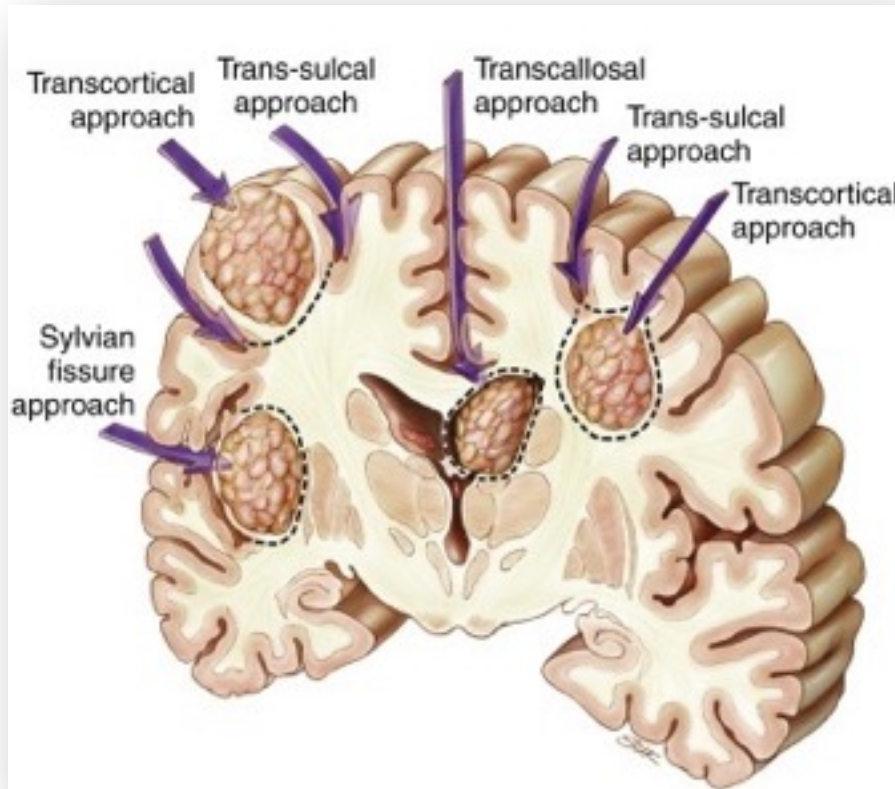




Different localizations
of Brain Metastases

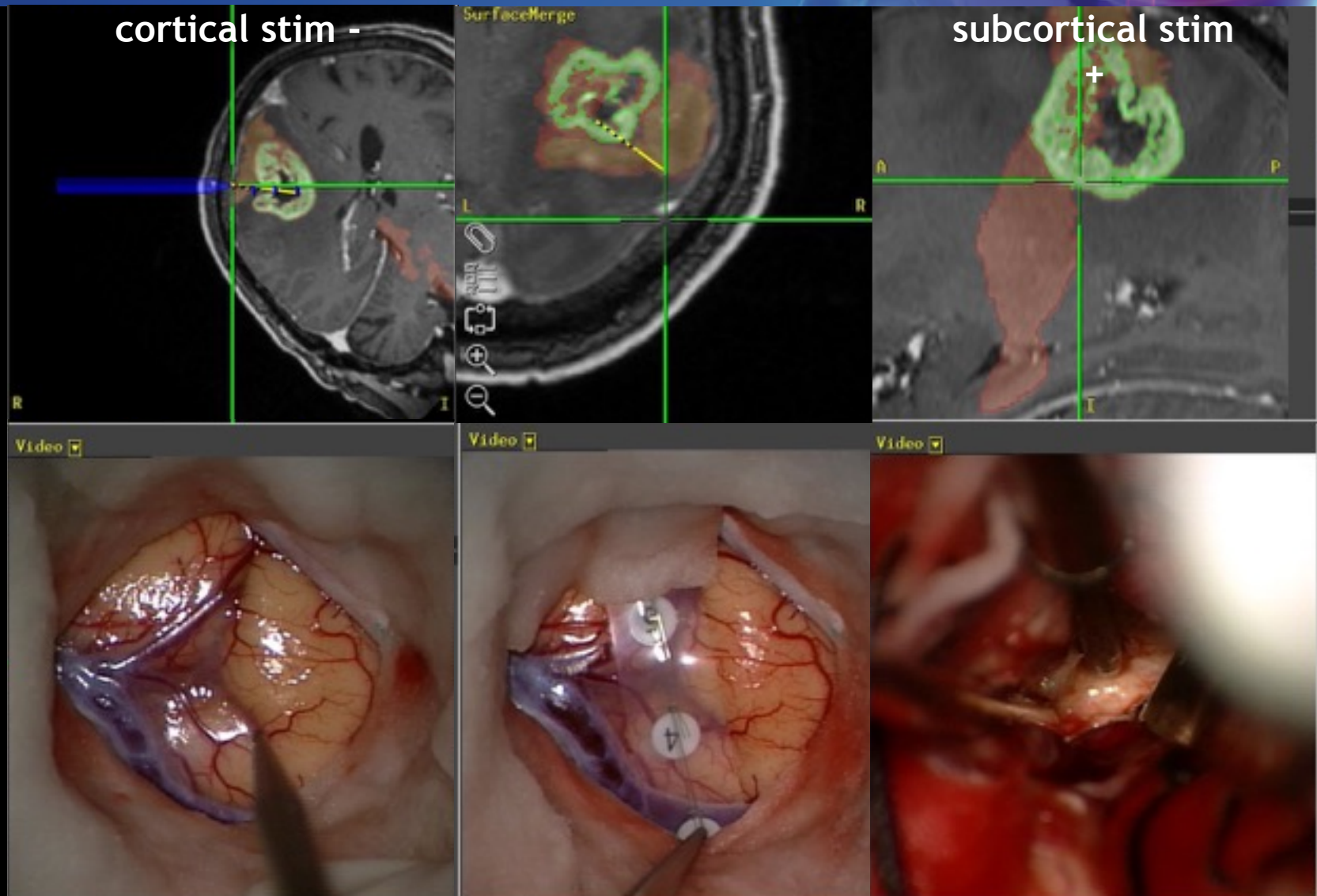
Neurosurgical Resection

Different approaches



Neurosurgical Resection

Different intraoperative techniques



Challenge of Modern Neurosurgical Resection of BM



Invasion patterns in brain metastases of solid cancers

Neuro-Oncology 15(12):1664–1672, 2013.

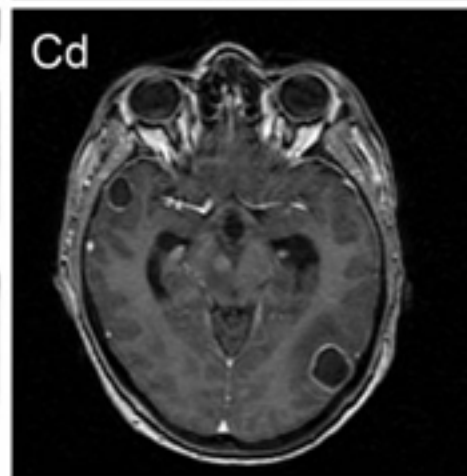
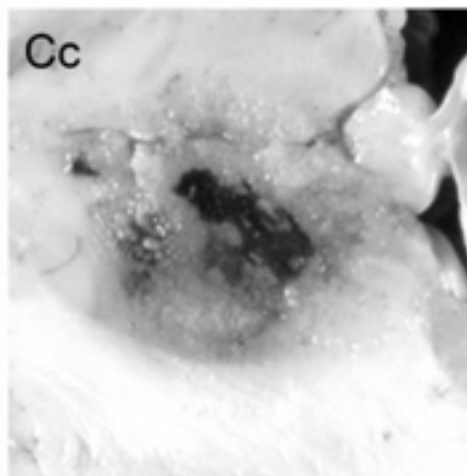
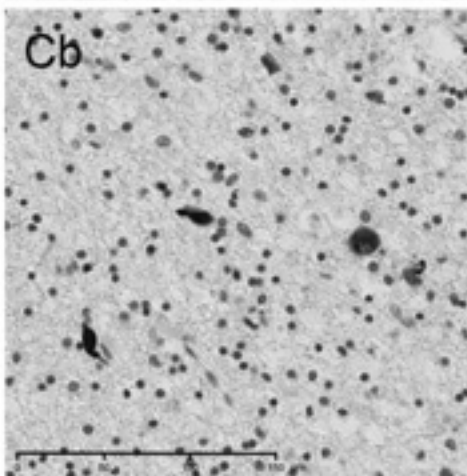
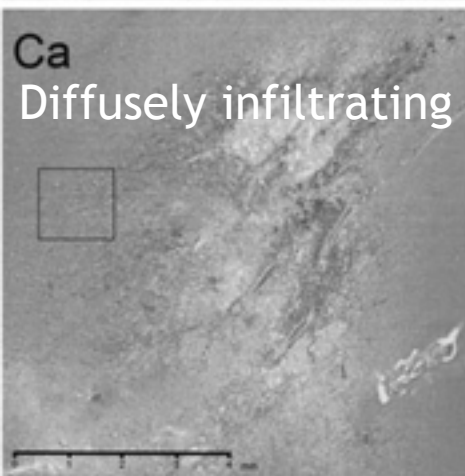
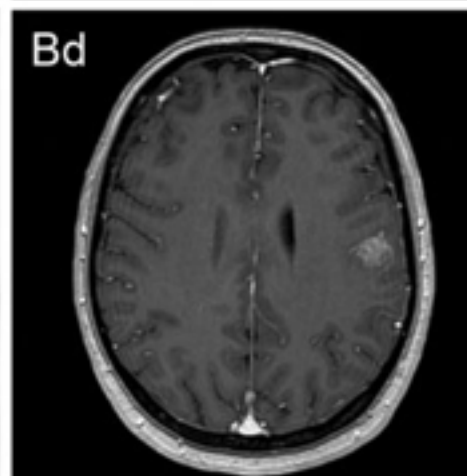
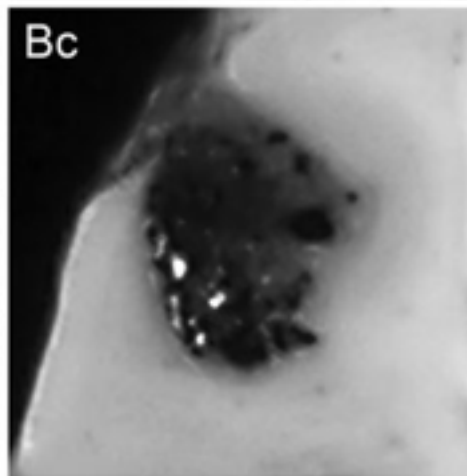
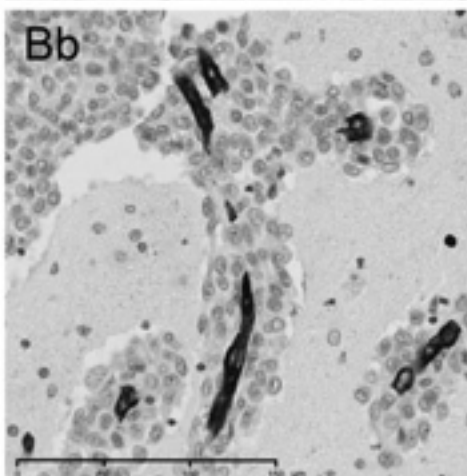
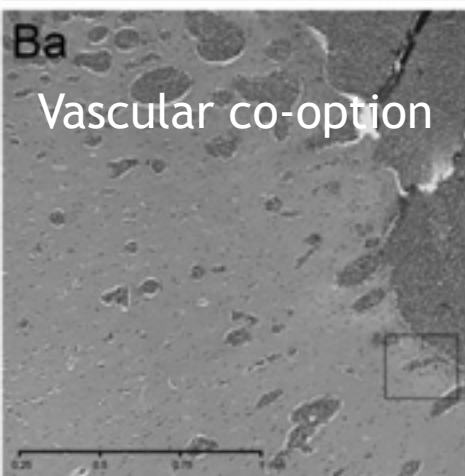
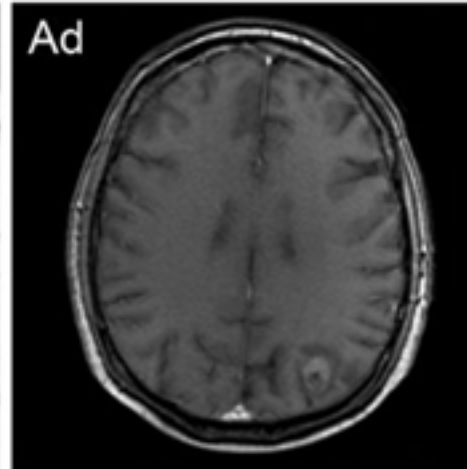
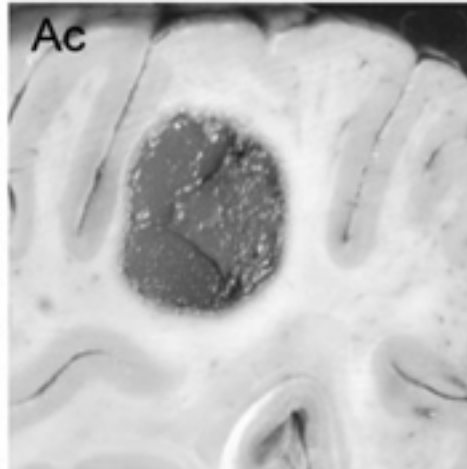
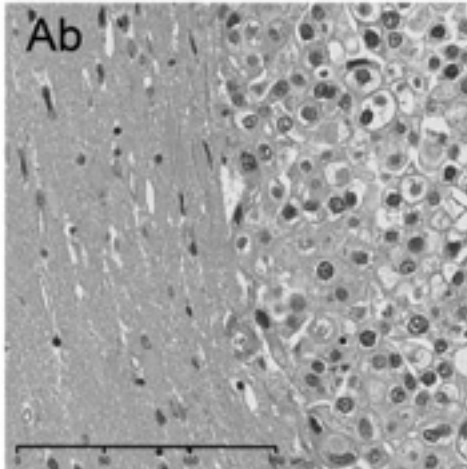
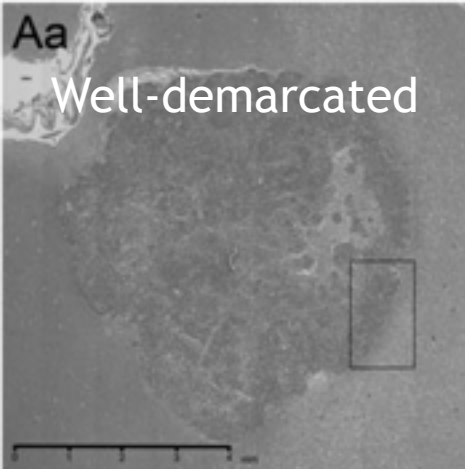
doi:10.1093/neuonc/not112

Advance Access publication September 30, 2013

Anna S. Berghoff, Orsolya Rajky, Frank Winkler, Rupert Bartsch, Julia Furtner, Johannes A. Hainfellner, Simon L. Goodman, Michael Weller, Jens Schittenhelm, and Matthias Preusser

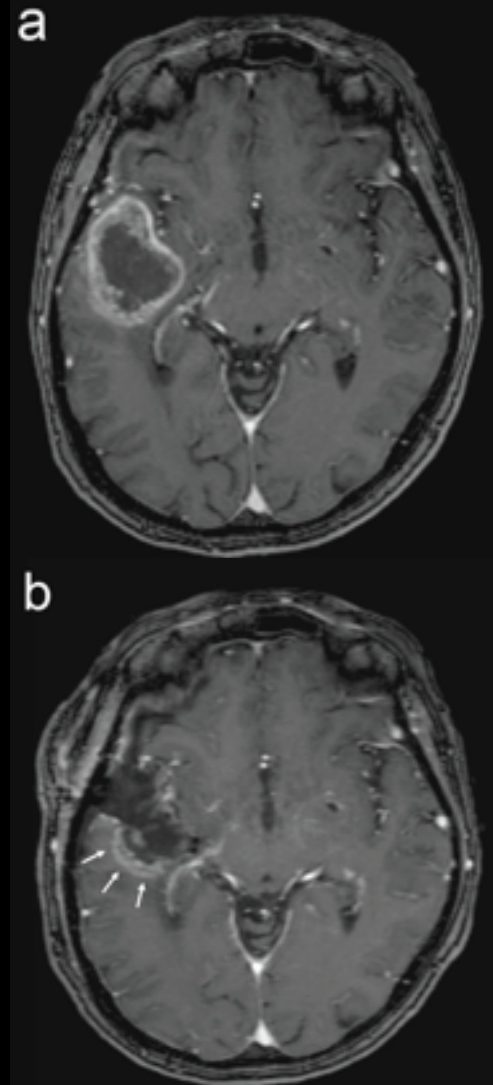
NEURO-ONCOLOGY

- 3 distinct invasion patterns of brain metastases
 - well-demarcated growth (51%)
 - vascular co-option (18%)
 - diffuse infiltration (32%)



Drawbacks of Brain Tumor Surgery

- iOP identification of brain tumor tissue is crucial to maximize extent of resection
- Insufficient iOP visualization of tumor tissue is not uncommon
- New innovative technique must be developed for iOP visualization of brain tumor tissue
- Photodynamic Diagnosis



Photodynamic Diagnosis (PDD)

Herley was able to differentiate between **benign** and **malignant breast lesions** using PDD

1944

1900

1950

2000

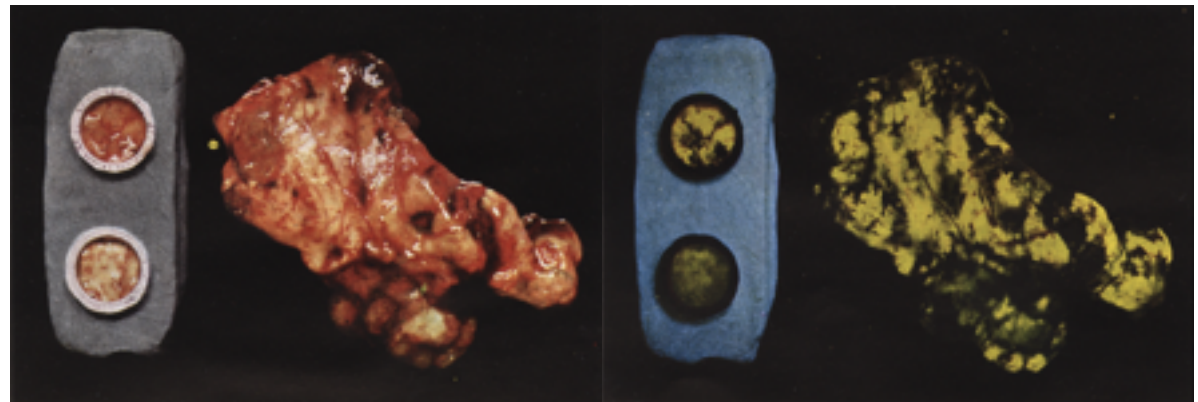
1934

Danckwortt first described the **visualization** of **malignant tissue** by PDD using different **fluorescent dyes** and **ultraviolet light**

1948

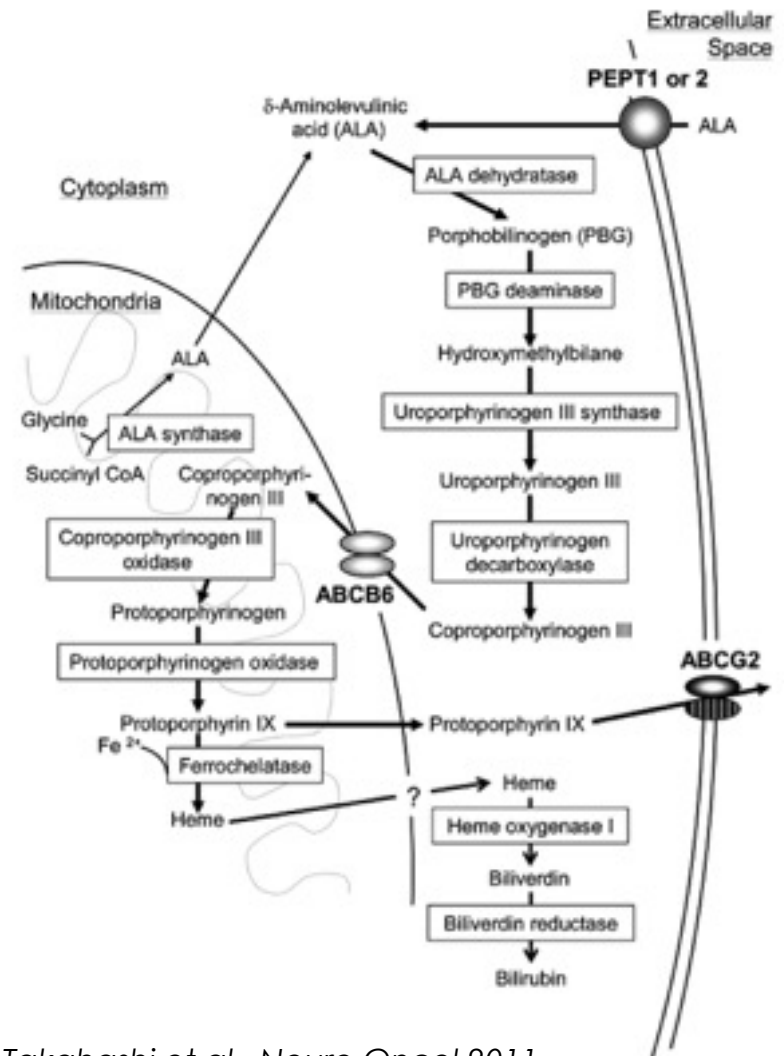
Moore reported the **use of PDD** with **Fluorescein** also during **neurosurgical procedures**

No wide acceptance!



5-Aminolevulinic Acid (5-ALA)

- **5-ALA:** New fluorescent dye for iOP visualization of different tumor tissues
- Since **1992** used in different surgical disciplines
- Precursor of the heme biosynthesis
- Oral administration
- Accumulation of fluorescing protoporphyrin IX (PpIX) in malignant tumor tissue



5-ALA in Neurosurgery



Stummer reported the first series of **52 consecutive glioblastomas** that underwent **5-ALA fluorescence-guided resection**



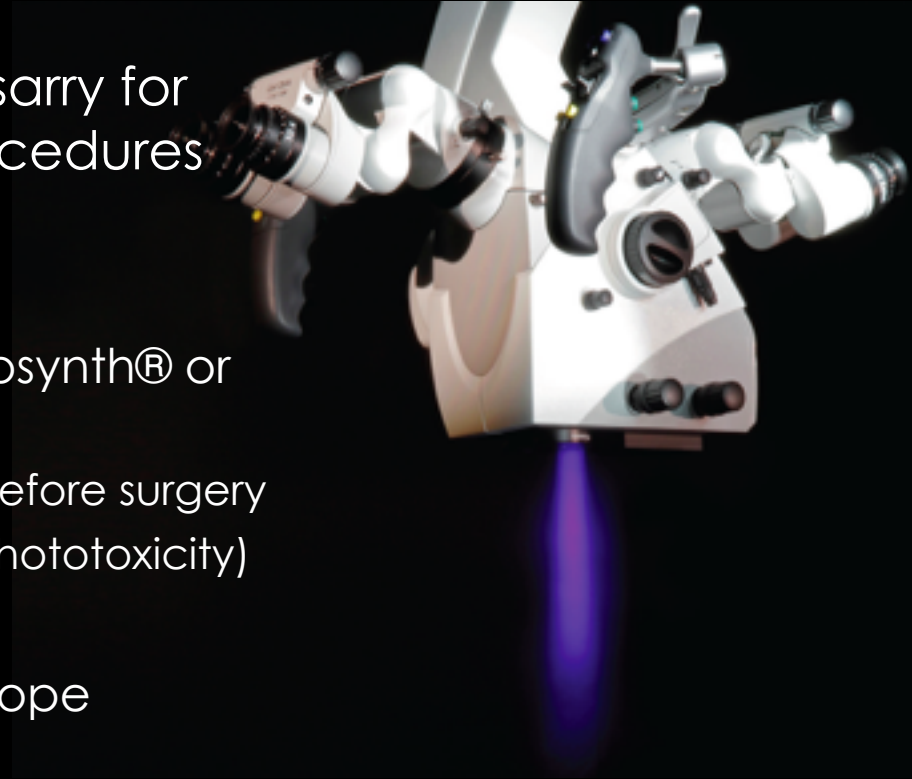
Stummer described the **first application of 5-ALA during resection** of suspected malignant gliomas

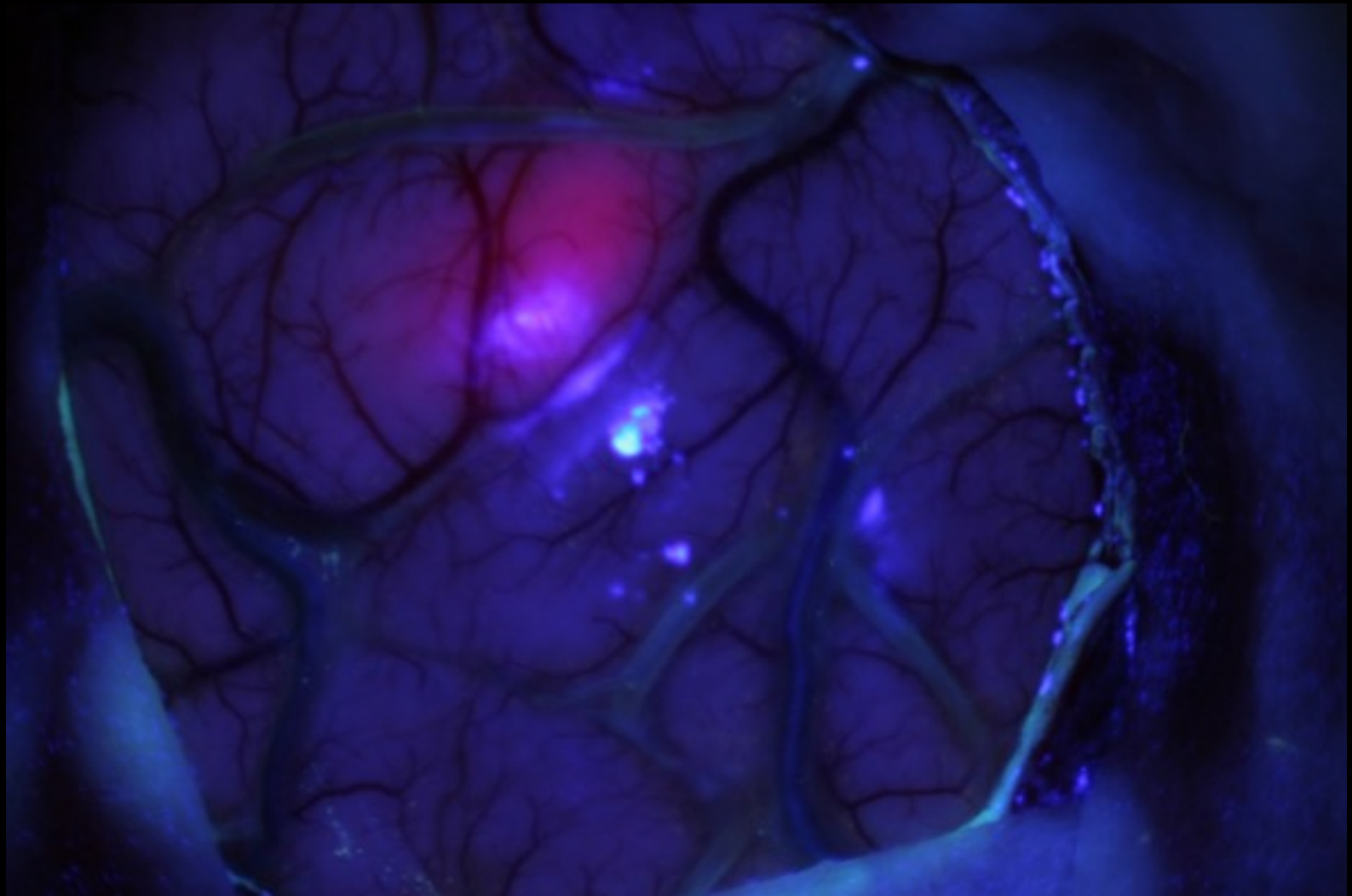
Multicenter phase III trial on malignant gliomas (5-ALA vs. white light resection):

- Significantly higher frequency of **complete resection** in 5-ALA group (65% vs. 36%)
- Significantly **prolonged progression-free survival** in the 5-ALA group (41% versus 21%)

5-ALA at Medical University Vienna

- Specific preparations are necessary for 5-ALA fluorescence-guided procedures
 - Specific training course (EU)
 - Oral administration of 5-ALA (Biosynth® or Gliolan®)
 - 20mg/kg bodyweight 3 hours before surgery
 - Protection from light sources (phototoxicity)
 - Modified neurosurgical microscope
- Since december 2007 fluorescence-guided procedures at our department (>800 cases)

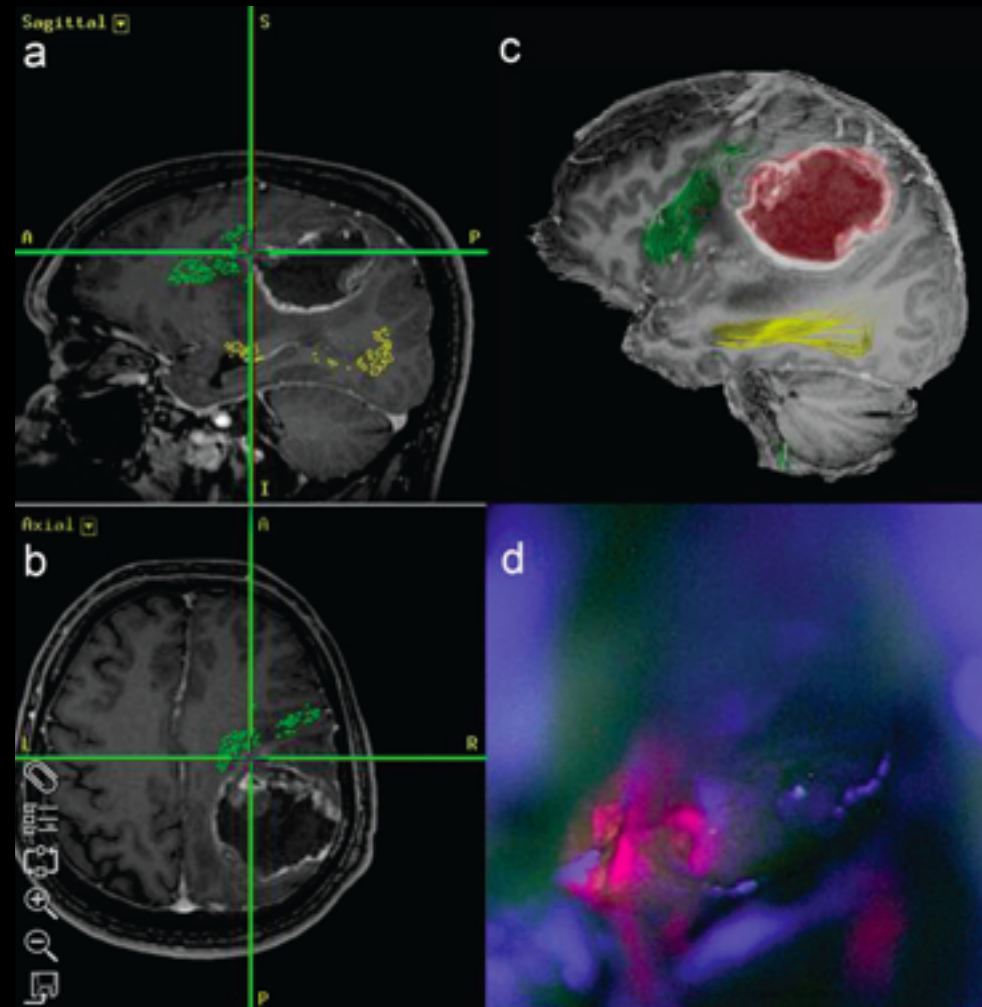




Preservation of Neurological Function during Fluorescence-guided Procedures

To avoid neurological deficits:

- Navigation system
- Multimodality image (DTI, fMRI)
- Electrophysiological monitoring
- Awake surgery

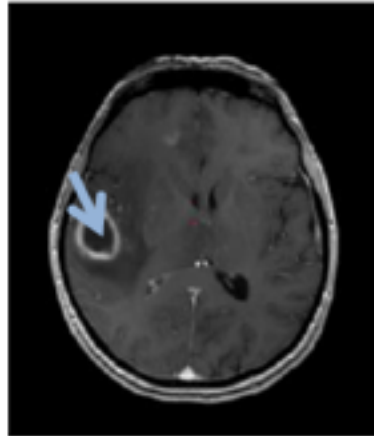


Different fluorescence qualities

Malignant Gliomas

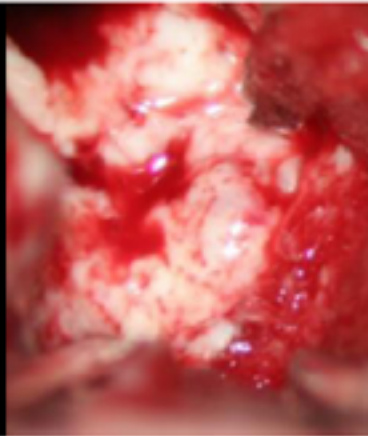


MRI T1+CE



core: no CE

white light



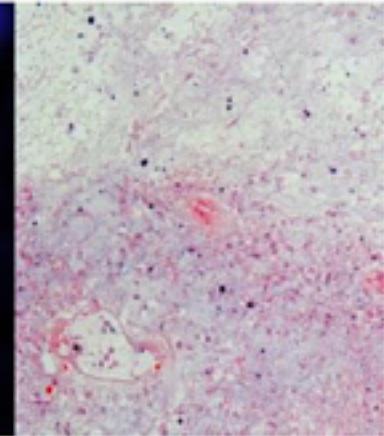
necrosis

PpIX fluorescence

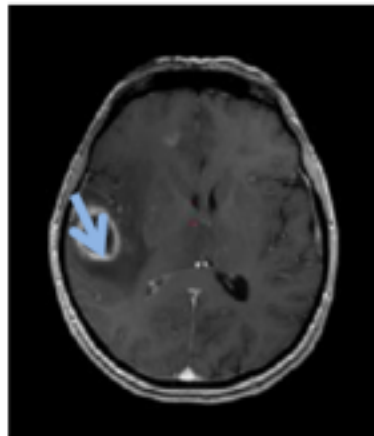


no fluorescence

histopathology



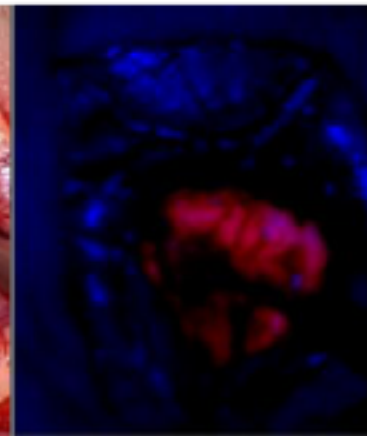
necrosis



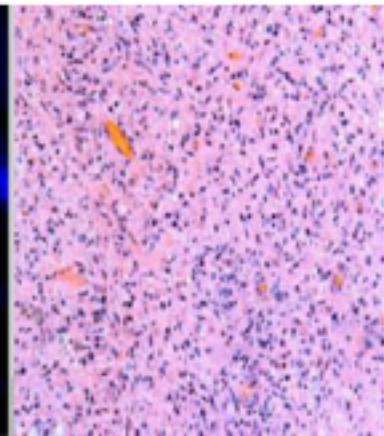
rim: CE



greyish, soft: tumor



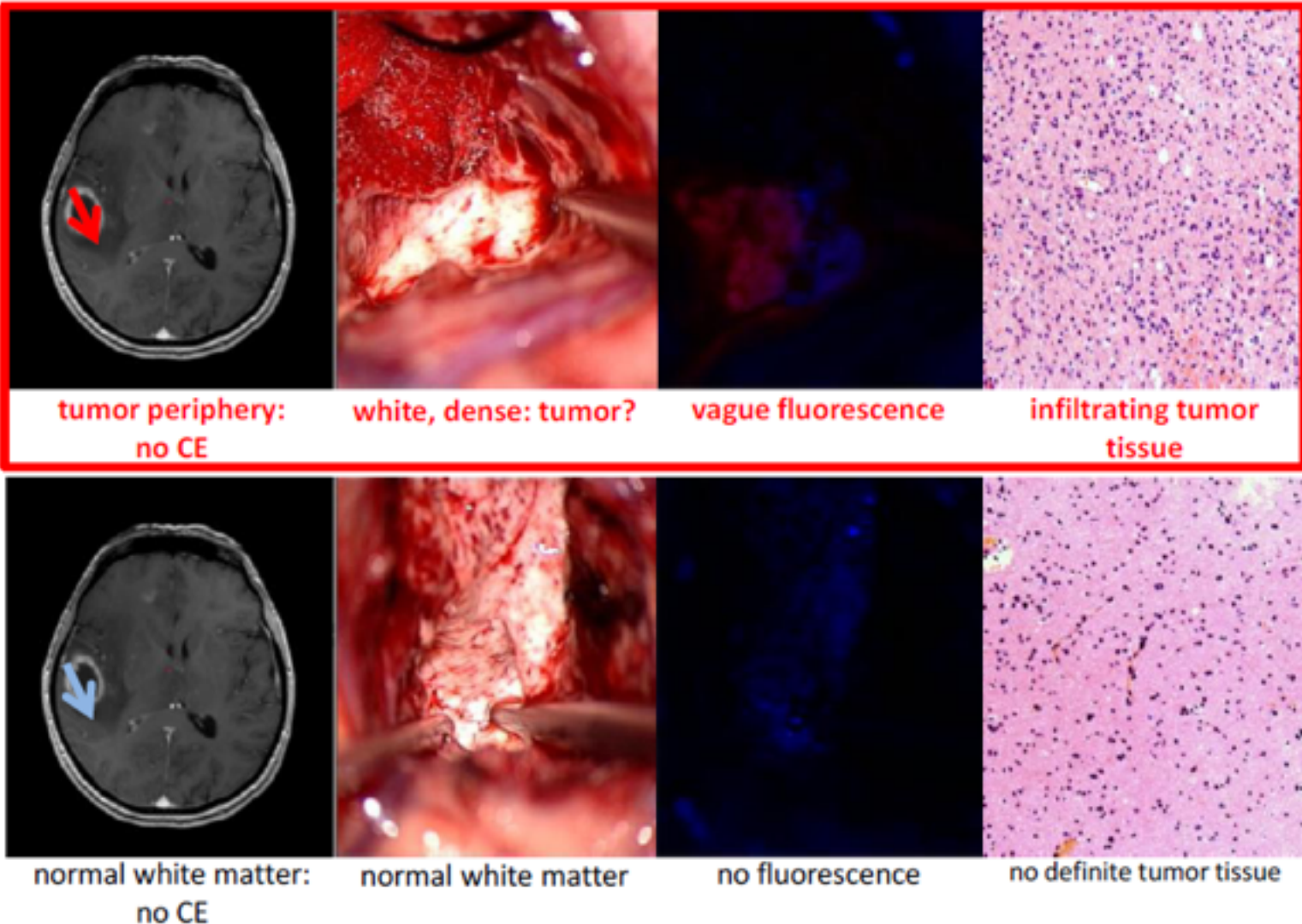
strong fluorescence



compact tumor tissue

Different fluorescence qualities

Malignant Gliomas



High PPV of 5-ALA for Detection of tumor tissue

TABLE 1. Studies With Sensitivity, Specificity, Positive and Negative Predictive Values of 5-ALA-Induced Fluorescence and Malignant Glioma Tissue^a

Publication	n Patients	Included Tumor Entities	Newly Diagnosed/Recurrent Tumors	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Yamada et al ²³ (2015)	97	HGG	Newly + recurrent	95	53	92	69
Coburger et al ²¹ (2014)	34	GBM	Newly + recurrent	91	80	99	22
Stummer et al ²² (2014)	33	HGG	Newly + recurrent	—	—	Overall 96	40
						Strong PpIX 100	
						Vague PpIX 95	
Pancani et al I ¹⁵ (2012)	23	GBM	Newly	91	89	89	91
Pancani et al II ¹⁶ (2012)	18	GBM	Newly	91	89	88	91
Diez Valle et al ¹⁸ (2011)	36	GBM	Newly + recurrent	—	—	Strong PpIX 100	66
						Vague PpIX 97	
Idoate et al ¹⁷ (2011)	30	GBM	Newly + recurrent	—	—	Solid tumor 100	67
						Invasive tumor 97	
Roberts et al ¹⁹ (2011)	11	GBM	Newly	75	71	95	26
Stummer et al ³ (2000)	52	GBM	Newly + recurrent	89	96	99	50

^aGBM, Glioblastoma; HGG, High-grade glioma (WHO grade III + IV); NPV, negative predictive value; PPV, positive predictive value; PpIX, protoporphyrin IX fluorescence.

Value of 5-ALA in High-Grade Gliomas

➔ @ Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial

Lancet Oncol 2006; 7: 392-401

Walter Stummer, Uwe Pichlmeier, Thomas Meinel, Otmar Dieter Wiestler, Friedhelm Zanella, Hans-Jürgen Reulen, for the ALA-Glioma Study Group*

- **Significantly increased rate of complete resection** of the contrast-enhancing tumor in the 5-ALA group (65%) vs. the conventional microsurgical control group (36%)
- **Significantly prolonged progression-free survival** was observed in the **5-ALA group** compared to white light alone with **cumulative 6-months progression-free survival rates of 41% versus 21%** ($p < 0.01$)

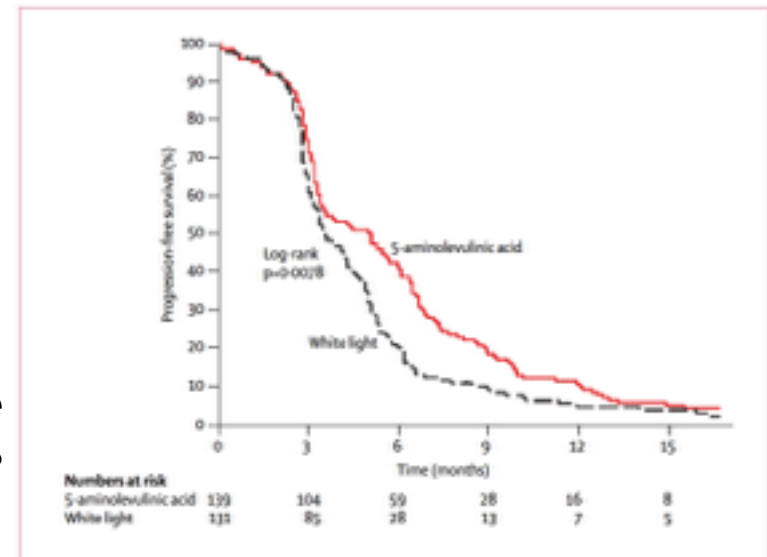


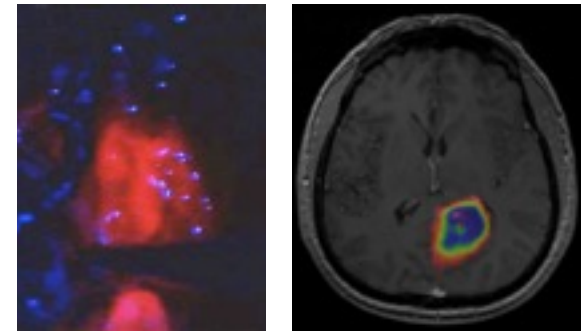
Figure 2: Progression-free survival by surgical group

Value of 5-ALA in suspected Low-grade Gliomas



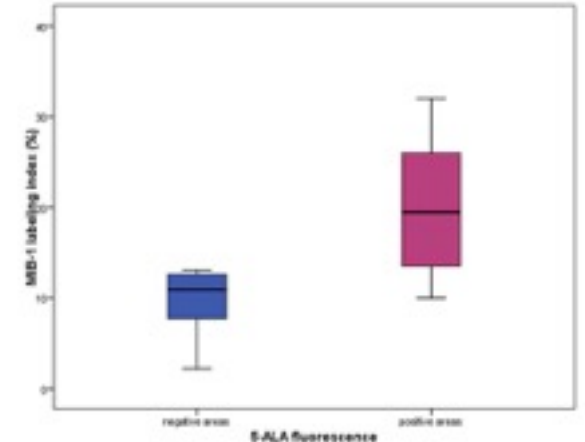
Focal PpIX fluorescence correlates with

- WHO °III histology
- PET_{max}
- Increased proliferation rate (MIB-1)
- WHO criteria of anaplasia



Histopathological criteria					
Mitosis	absent	29	(91%)	2	(7%)
	few	3	(9%)	14	(52%)
	many	0	(0%)	11	(41%)
Cell density	low	14	(44%)	1	(4%)
	moderate	15	(47%)	17	(63%)
	high	3	(9%)	9	(33%)
Nuclear pleomorphism	low	21	(66%)	2	(7%)
	moderate	9	(28%)	16	(60%)
	high	2	(6%)	9	(33%)

Widhalm et al., PLoS ONE 2013



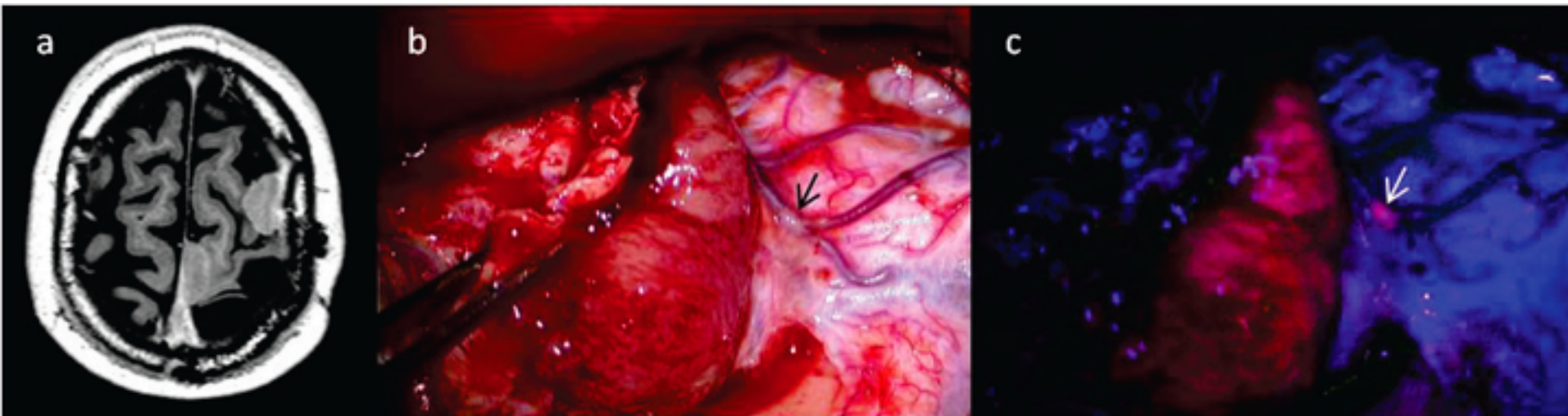
Widhalm et al., Cancer 2010

5-ALA enables improved precision of tissue sampling for histopathological grading and thus optimizes allocation of patients to adjuvant treatments

Value of 5-ALA in Meningiomas

Our data in > 200 meningiomas indicate that **5-ALA induced fluorescence** is a **promising marker** for **iOP visualization** of

- (Residual-) meningioma tissue
- Satellite lesions
- Bone flap infiltration

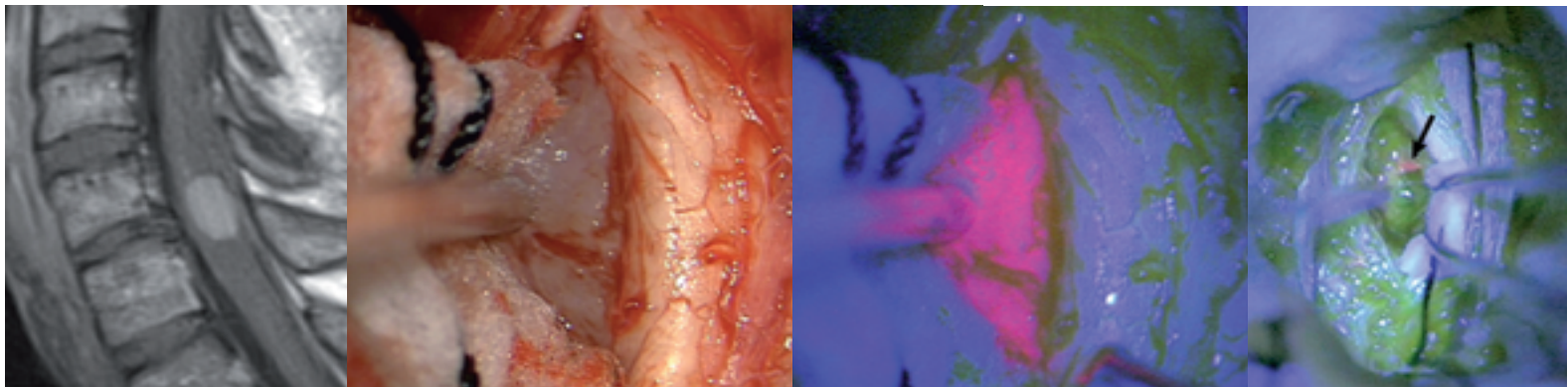


Value of 5-ALA in Spinal Tumors

Analysis of 5-aminolevulinic acid–induced fluorescence in 55 different spinal tumors

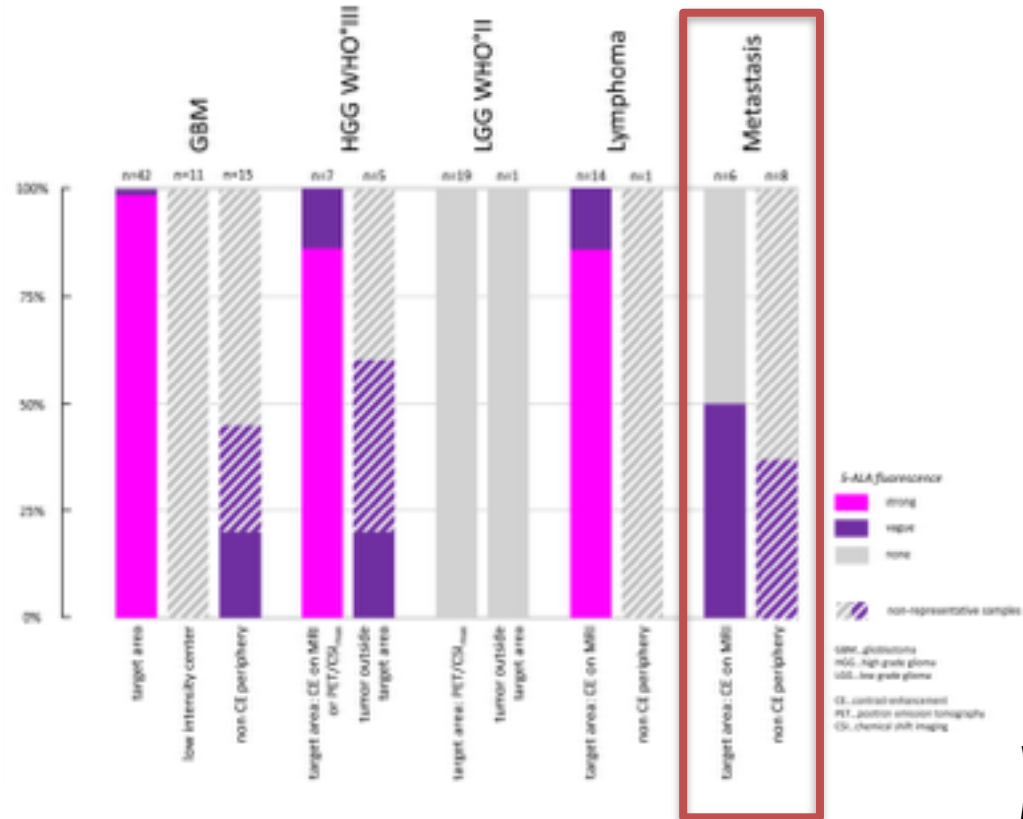
**MATTHIAS MILLESI, M.D.,^{1,3} BARBARA KIESEL, M.D.,^{1,3} ADELHEID WOEHRER, M.D., Ph.D.,^{2,3}
JOHANNES A. HAINFELLNER, M.D.,^{2,3} KLAUS NOVAK, M.D.,¹
MAURICIO MARTÍNEZ-MORENO, M.D.,¹ STEFAN WOLFSBERGER, M.D.,^{1,3}
ENGELBERT KNOSP, M.D.,^{1,3} AND GEORG WIDHALM, M.D., Ph.D.^{1,3}**

Neurosurg Focus / Volume 36 / February 2014



- 5-ALA induced fluorescence is able to visualize also a subgroup of spinal tumors (55% of cases).
- In intramedullary tumors, PpIX fluorescence is an useful tool for the detection of potential residual tumor foci.

Value of 5-ALA in Brain Tumor Biopsies



Widhalm et al., Neurosurg
Rev 2012

Strong 5-ALA fluorescence is a reliable and immediately available intraoperative marker of representative tumor tissue in stereotactic biopsies

Value of 5-ALA in Brain Metastasis

A stylized illustration of a human head in profile, facing left. The head is rendered in a translucent blue color. Inside the head, the brain is depicted with a vibrant, glowing orange and yellow color, suggesting neural activity or a specific focus. The background is a solid dark blue.

Although brain metastasis represents a frequent tumor in the routine neurosurgical practice, the value of 5-ALA in these tumors remain unclear.

Current study

5-ALA in brain metastasis



- Inclusion: Patients with resection of a brain metastasis
- 20 mg 5-ALA/kg bodyweight, 3h before anesthesia
- Modified neurosurgical microscope
- iOP tumor fluorescence status: strong, vague or negative
- 5-ALA fluorescence classified: homogenous or heterogenous
- Surrounding brain tissue investigated for the presence of fluorescence
- Histopathological tumor diagnosis (WHO criteria)

Patient characteristics & Histopathology of primary tumor

98 patients (2009 – 2015)

m:f ratio = 1 : 1,2

Median age 60y (range 27 – 83y)

Histopathology of primary tumor

29 Lung cancer

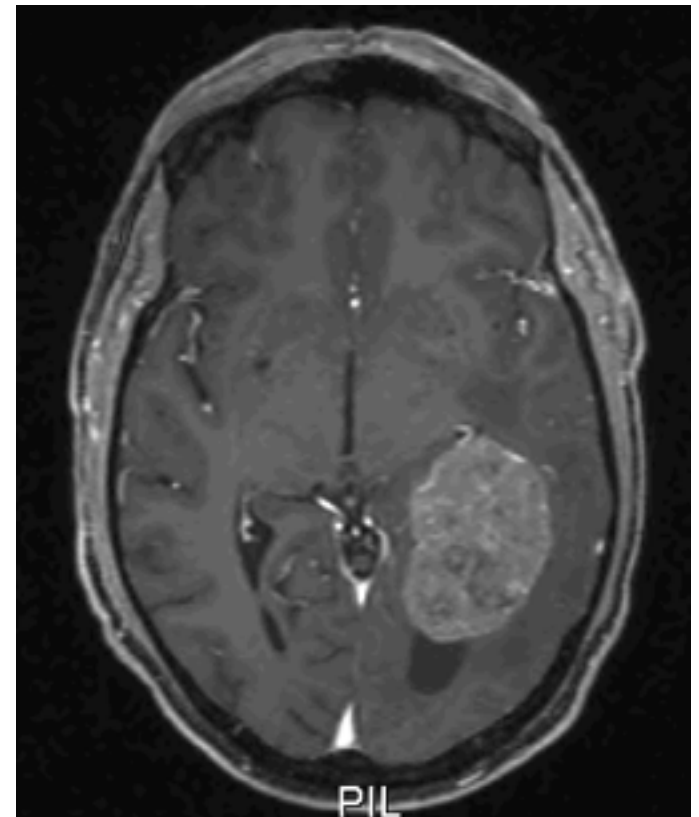
20 Breast cancer

14 Metastases of unknown primary

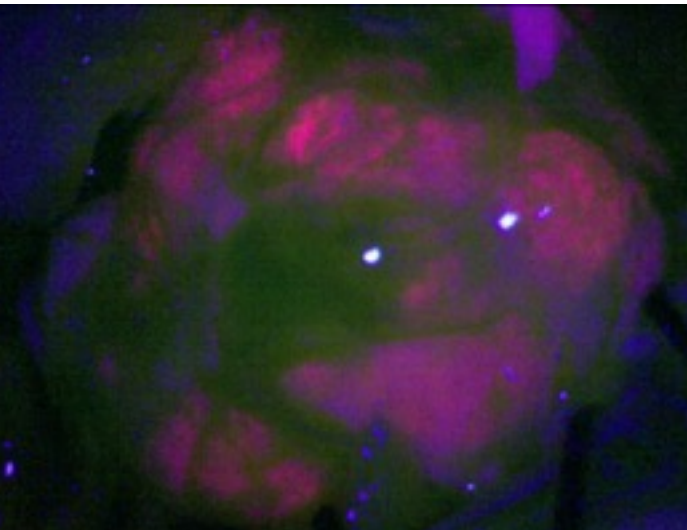
8 Melanoma

5 Renal cell carcinoma

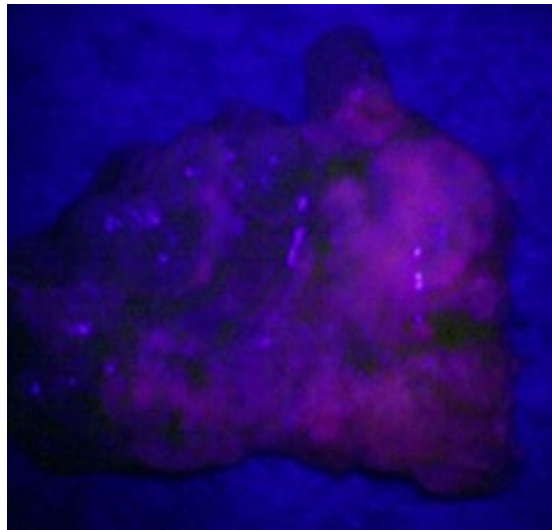
22 Others



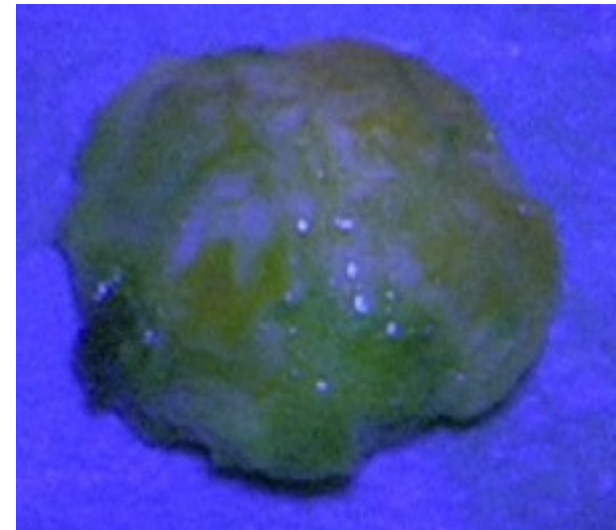
Different fluorescence patterns in brain metastases



5-ALA strong



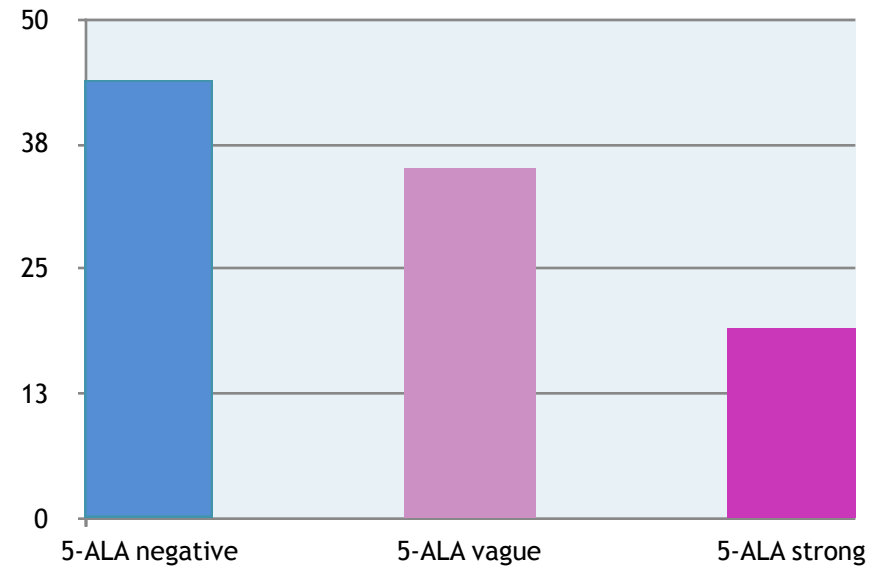
5-ALA vague



5-ALA negative

5-ALA in Brain Metastases

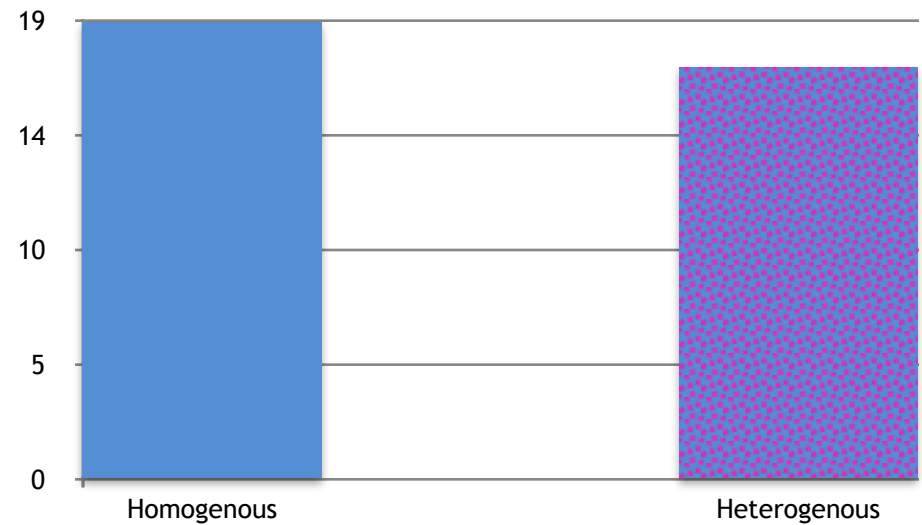
<i>n</i> =98	<i>n</i>	%
5-ALA negative	44	45%
5-ALA vague	35	19%
5-ALA strong	19	36%



5-ALA Fluorescence Homogeneity



<i>n</i> =36	<i>n</i>	%
Homogenous	19	53%
Heterogenous	17	47%

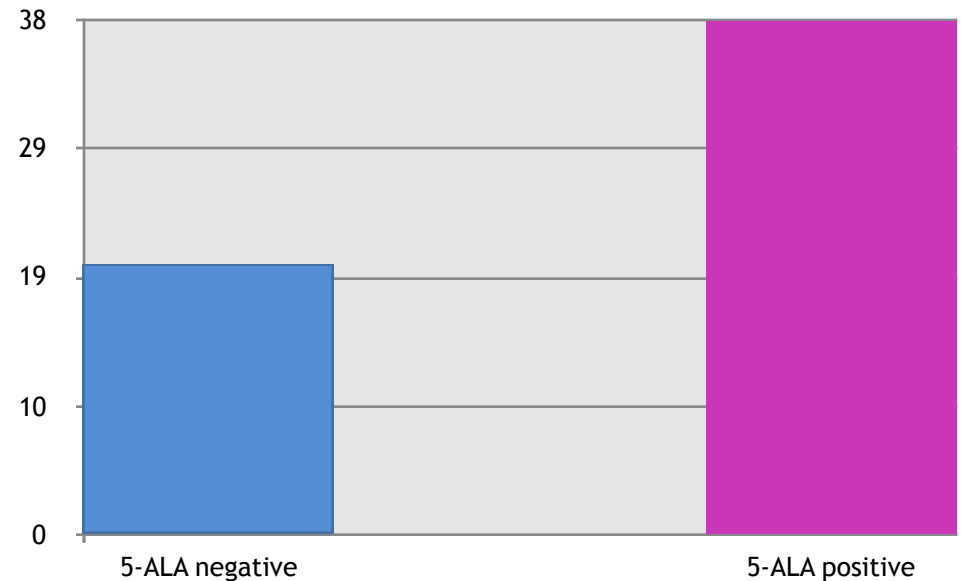


5-ALA Fluorescence

Surrounding brain tissue

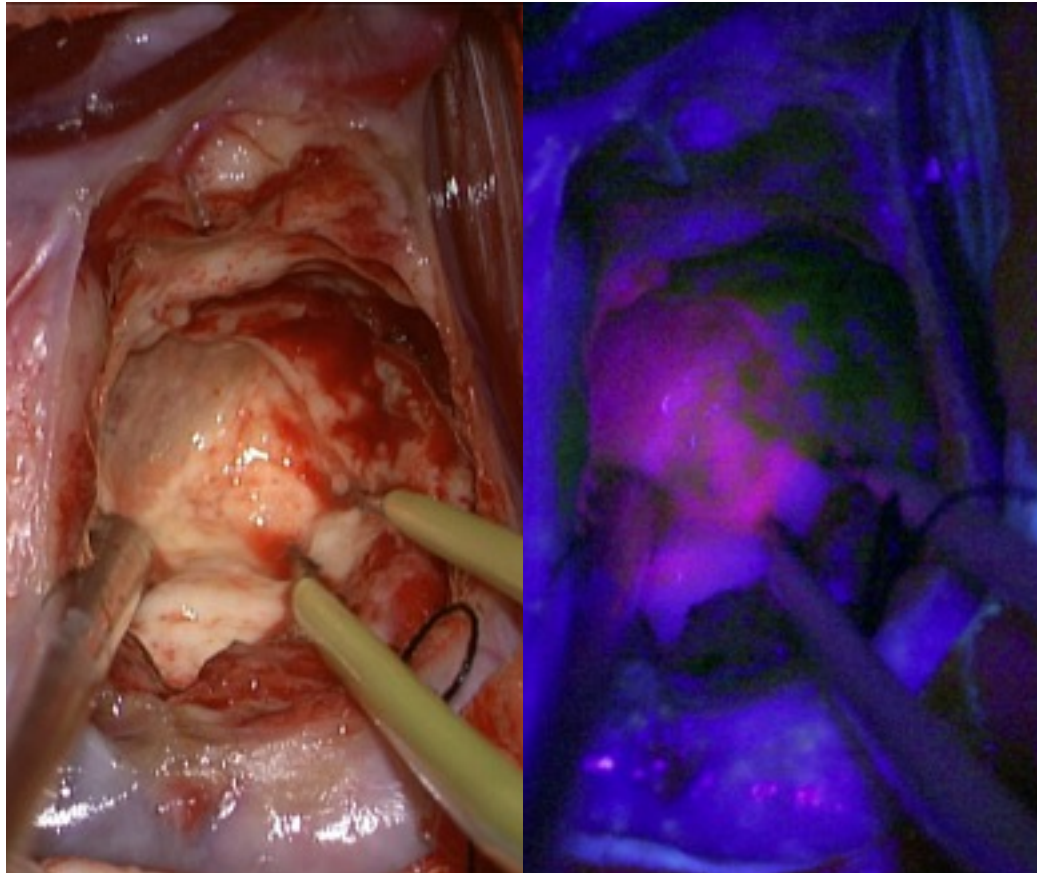


<i>n</i> =58	<i>n</i>	%
5-ALA negative	20	34%
5-ALA positive	38	66%

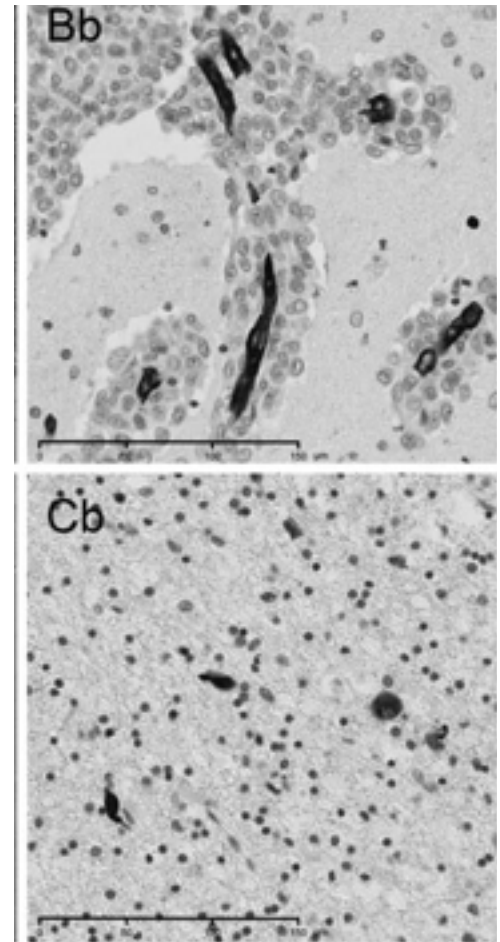


5-ALA Fluorescence

Surrounding brain tissue



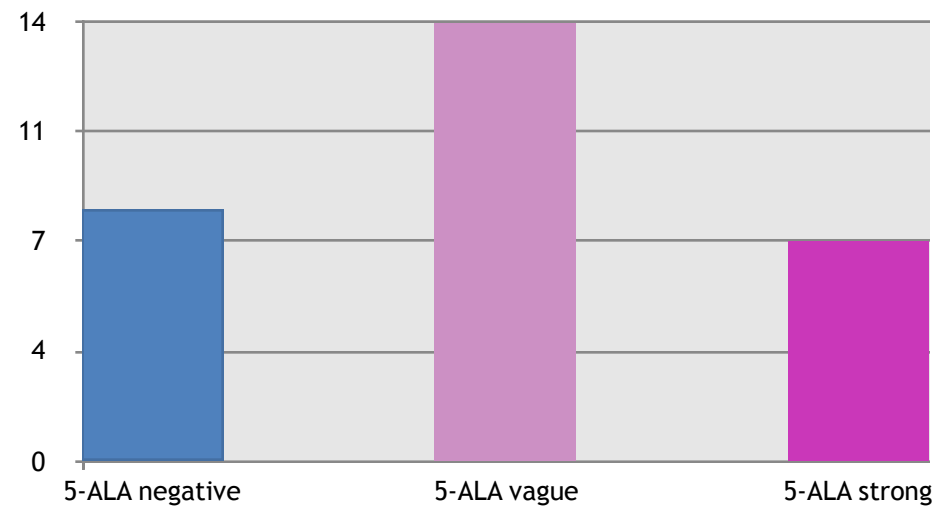
???



5-ALA in different Brain Metastases

Lung cancer

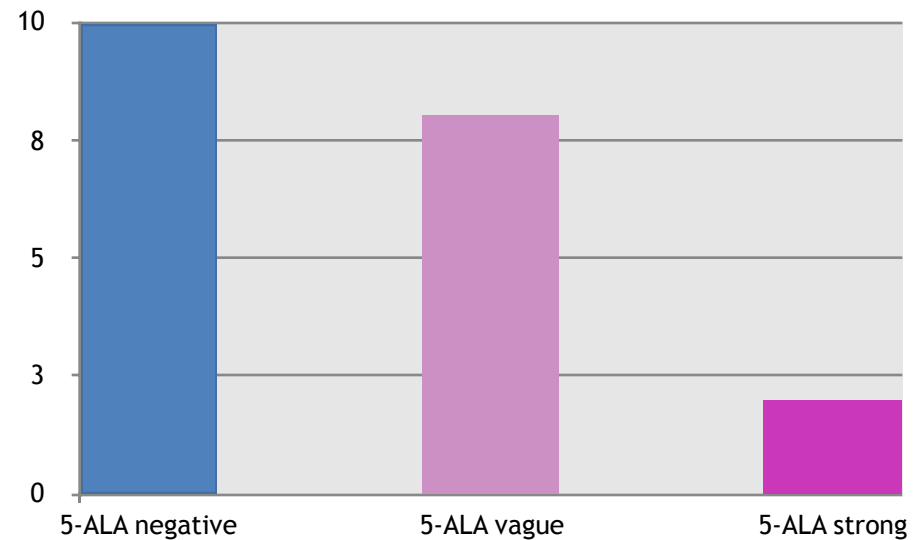
<i>n</i> =29	<i>n</i>	%
5-ALA negative	8	28%
5-ALA vague	14	48%
5-ALA strong	7	24%



5-ALA in different Brain Metastases

Breast cancer

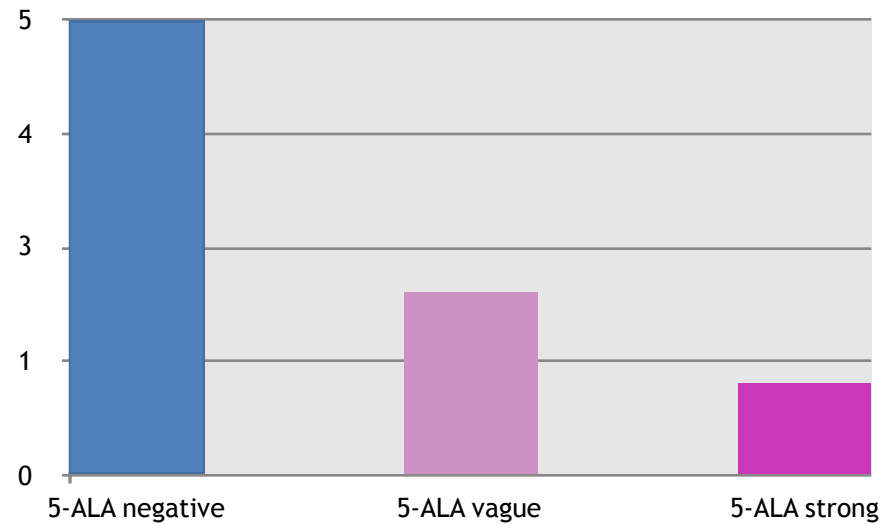
<i>n=20</i>	<i>n</i>	<i>%</i>
5-ALA negative	10	50%
5-ALA vague	8	40%
5-ALA strong	2	10%



5-ALA in different Brain Metastases

Melanoma

<i>n</i> =8	<i>n</i>	%
5-ALA negative	5	63%
5-ALA vague	2	12%
5-ALA strong	1	25%

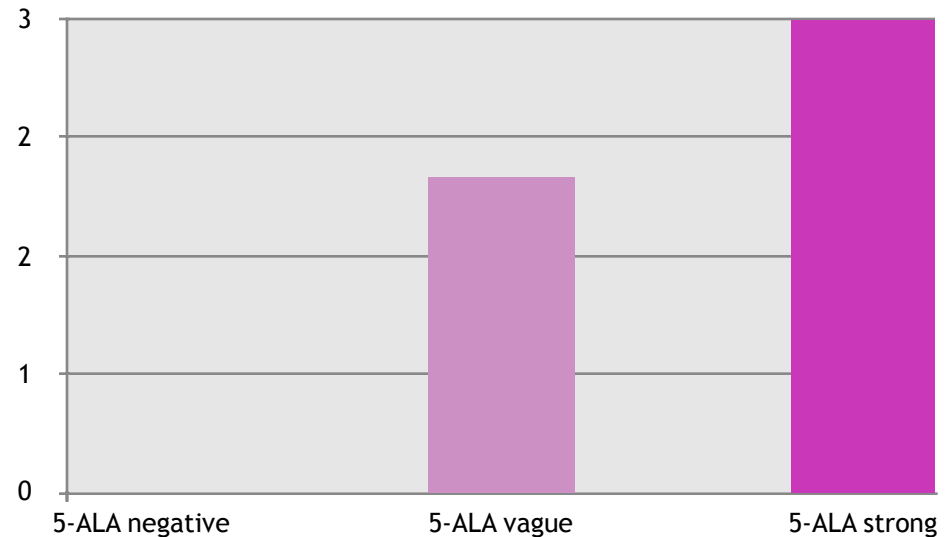


5-ALA in different Brain Metastases

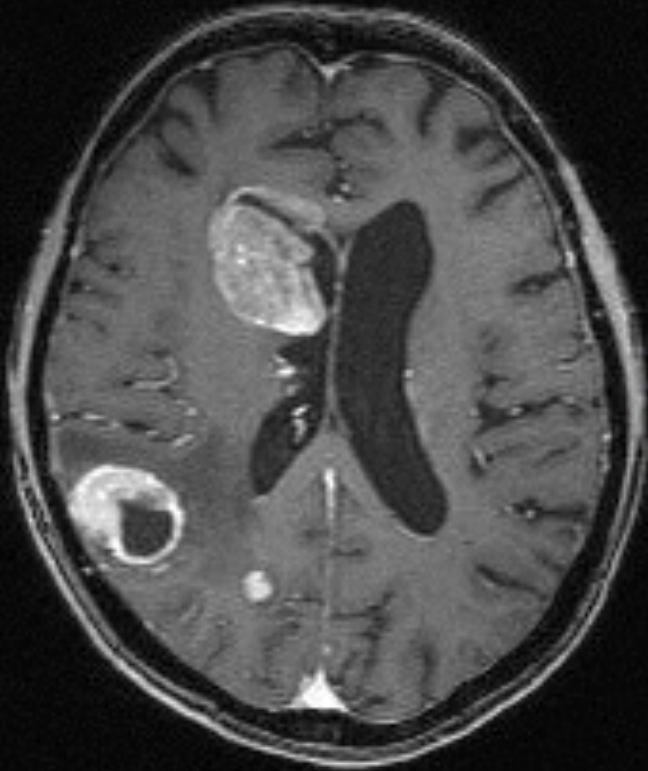
Renal Cell Carcinoma



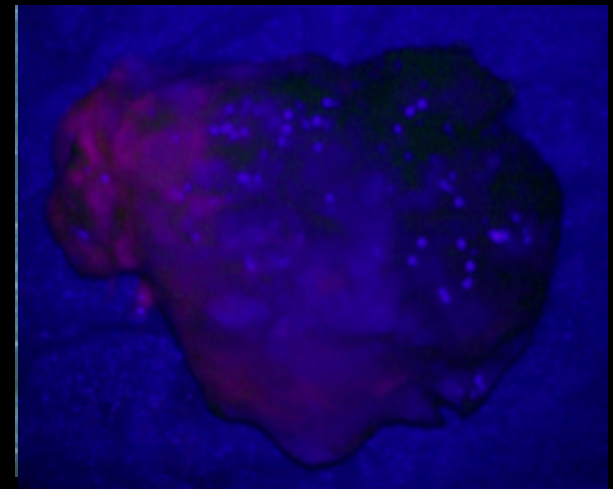
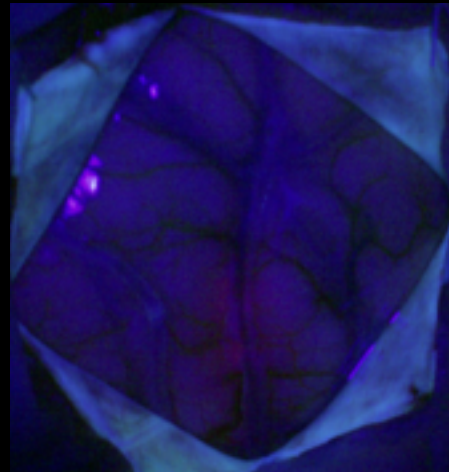
<i>n=5</i>	<i>n</i>	<i>%</i>
5-ALA negative	0	-
5-ALA vague	2	40%
5-ALA strong	3	60%



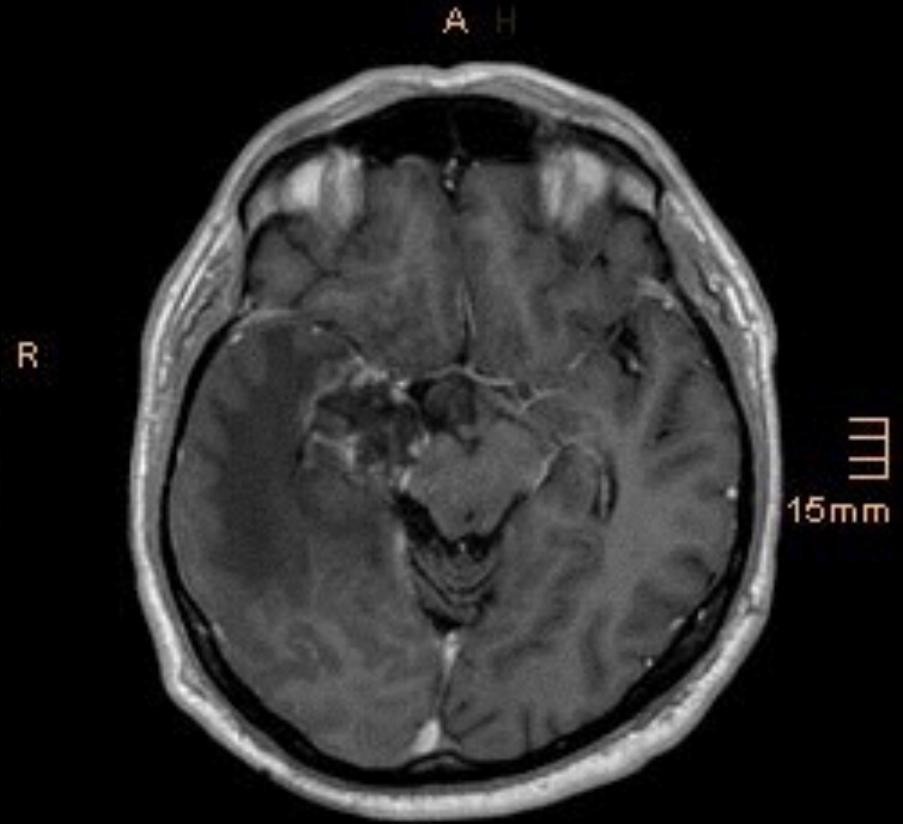
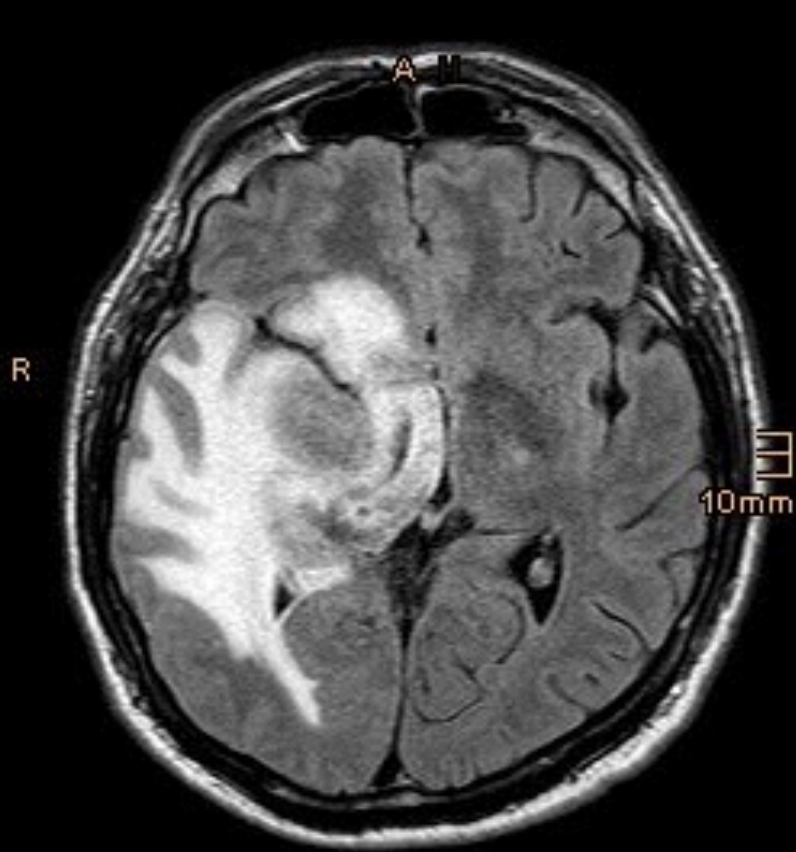
Intraoperative Differential diagnosis



A brain metastasis should be suspected if the tumor shows an heterogeneous fluorescence (negative and vague) and the surrounding brain tissue shows vague fluorescence



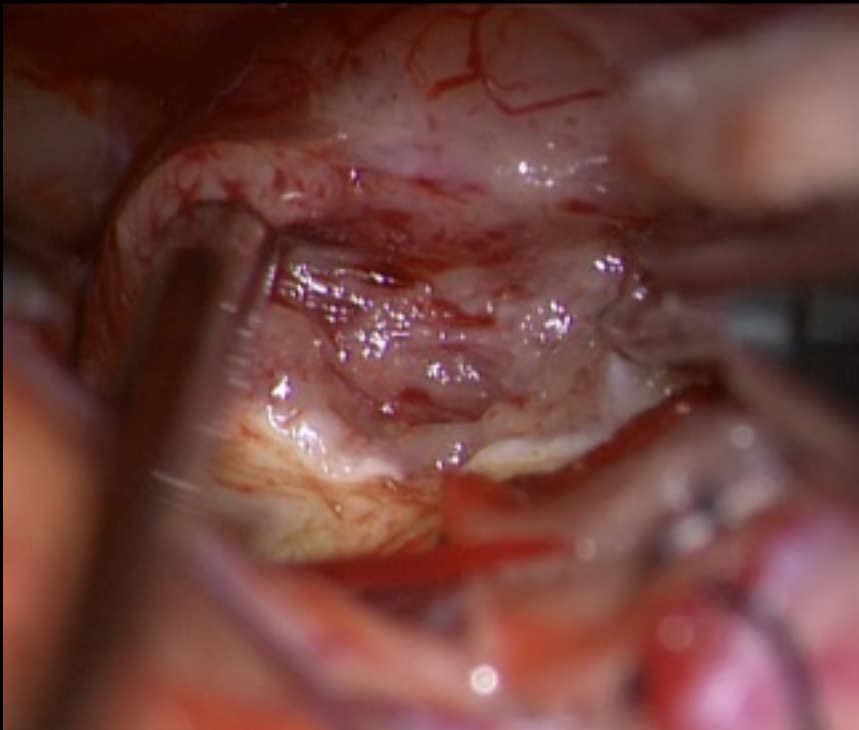
5-ALA in Radionecrosis



5-ALA in Radionecrosis



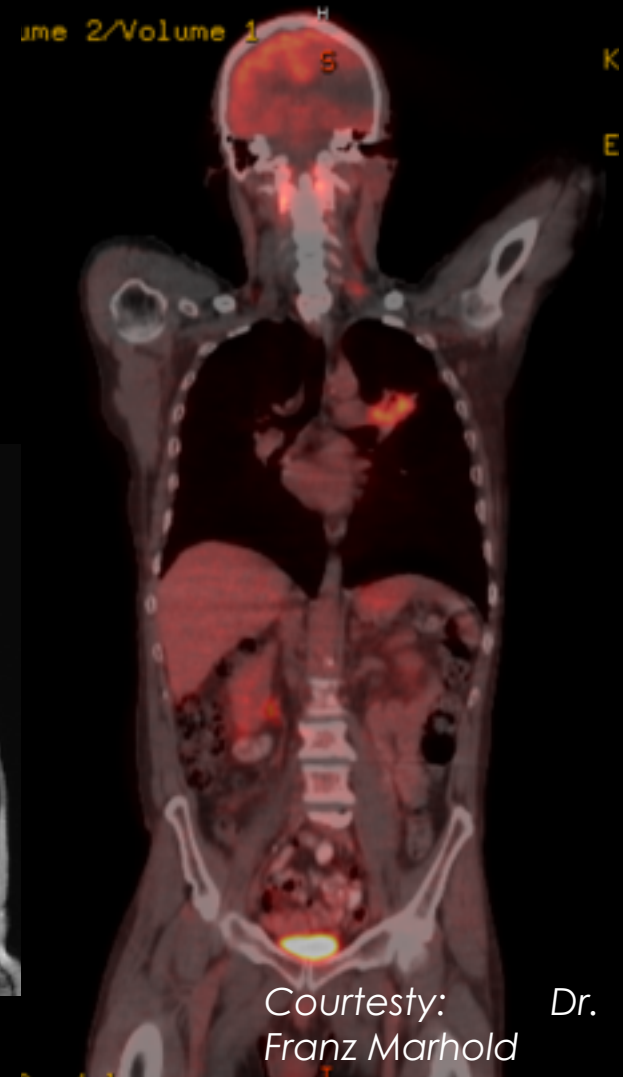
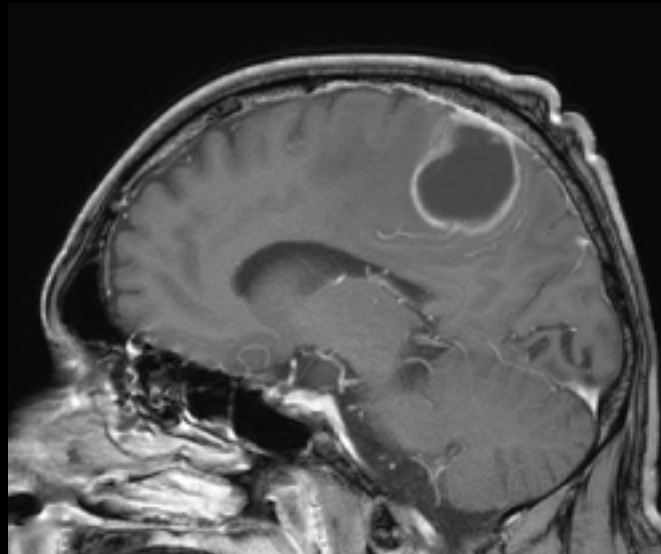
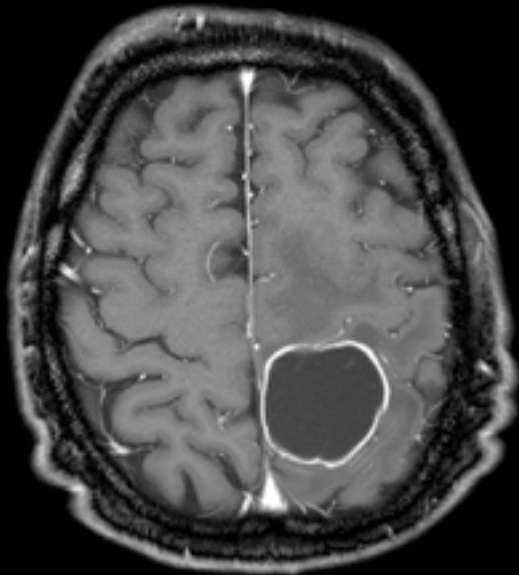
According to our experience 5-ALA fluorescence can also be observed in some cases of radionecrosis (normally vague fluorescence)



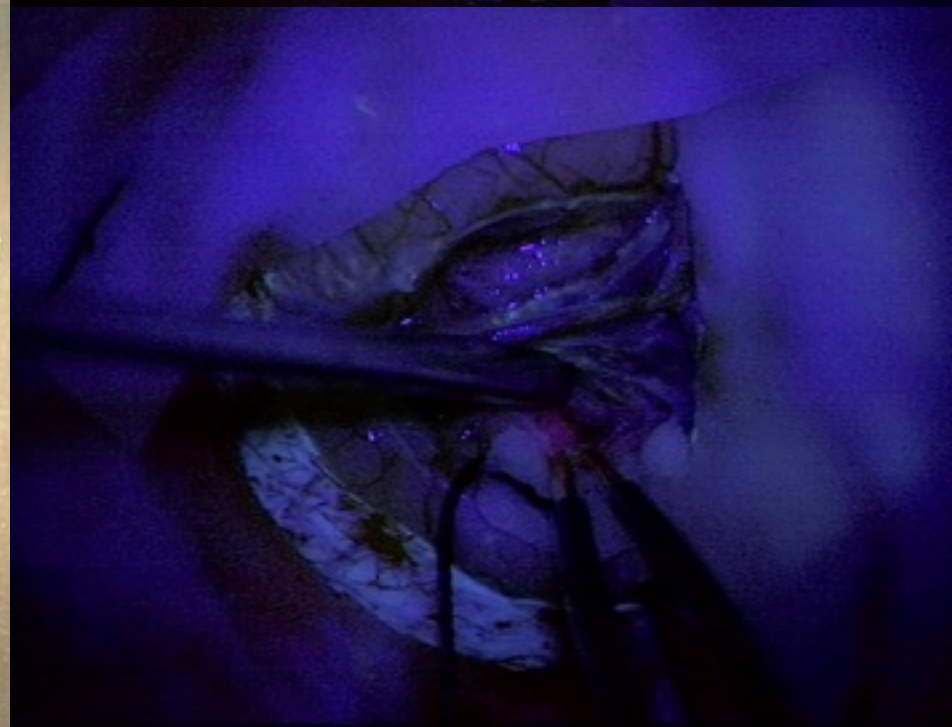
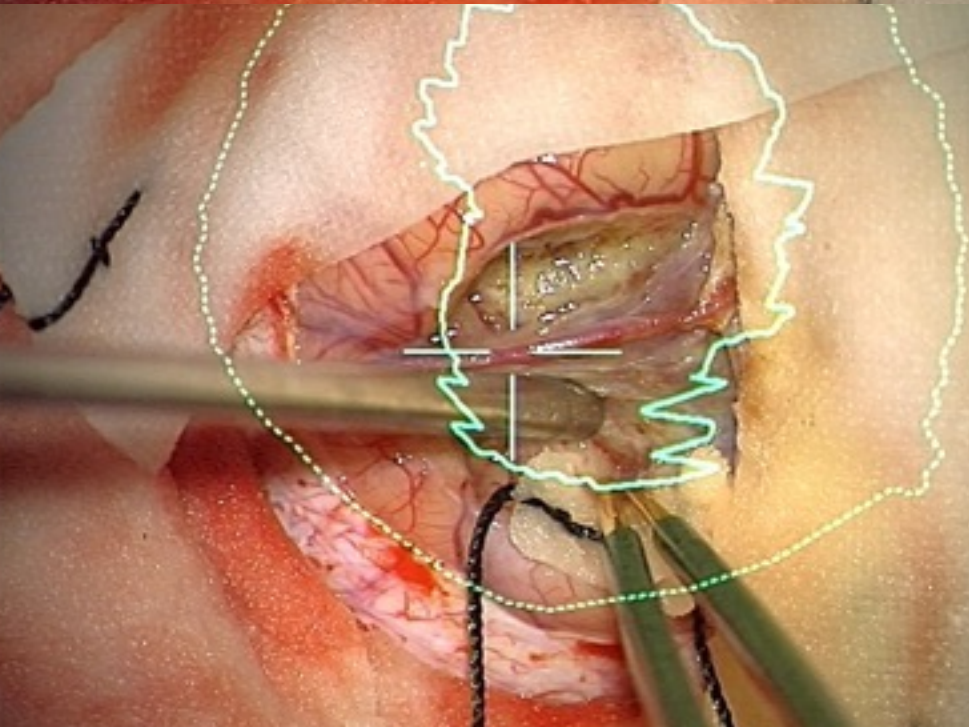
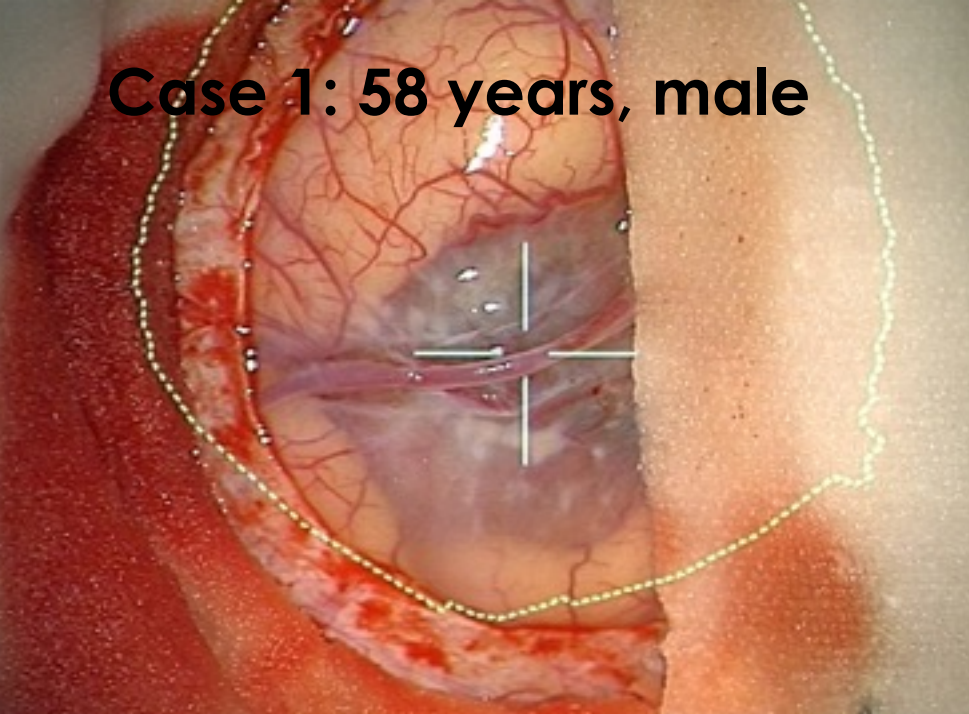
Case 1: 58 years, male



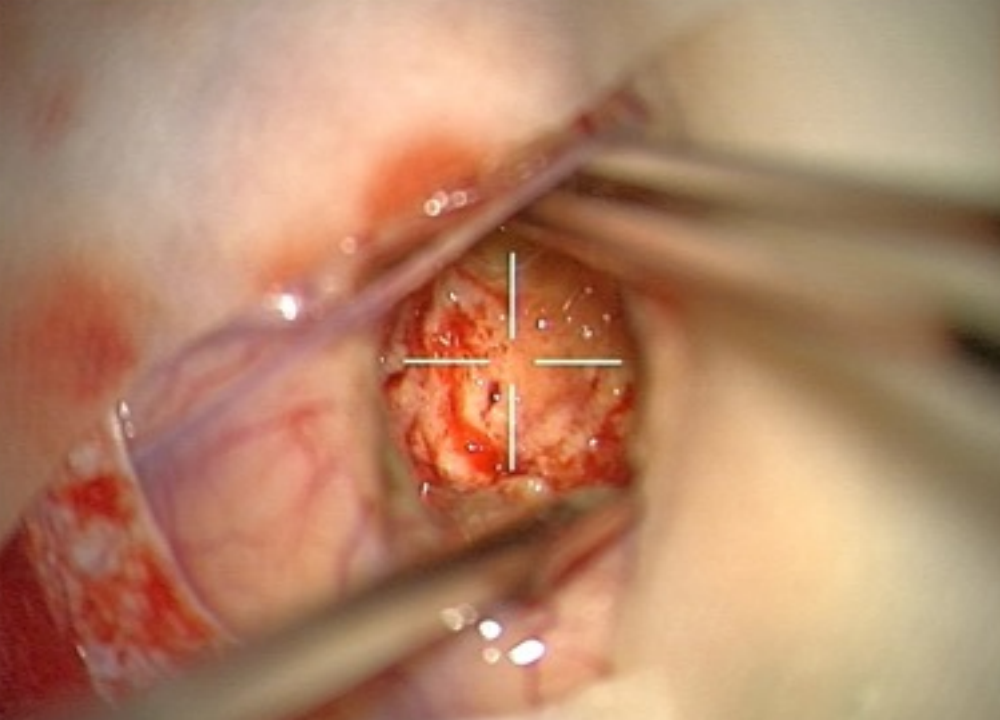
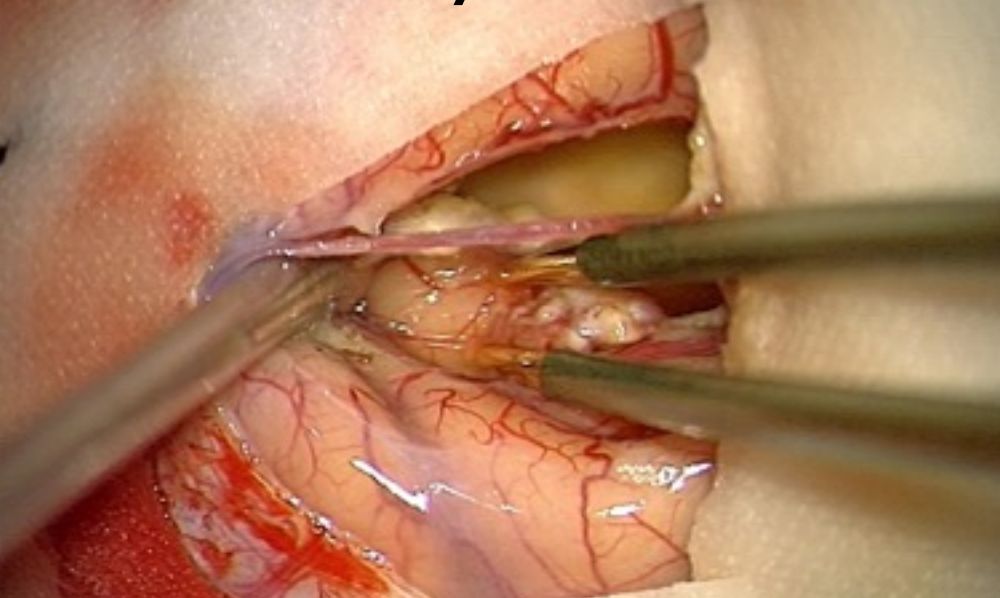
- Headache
- Left central tumor
- Lung cancer



Case 1: 58 years, male



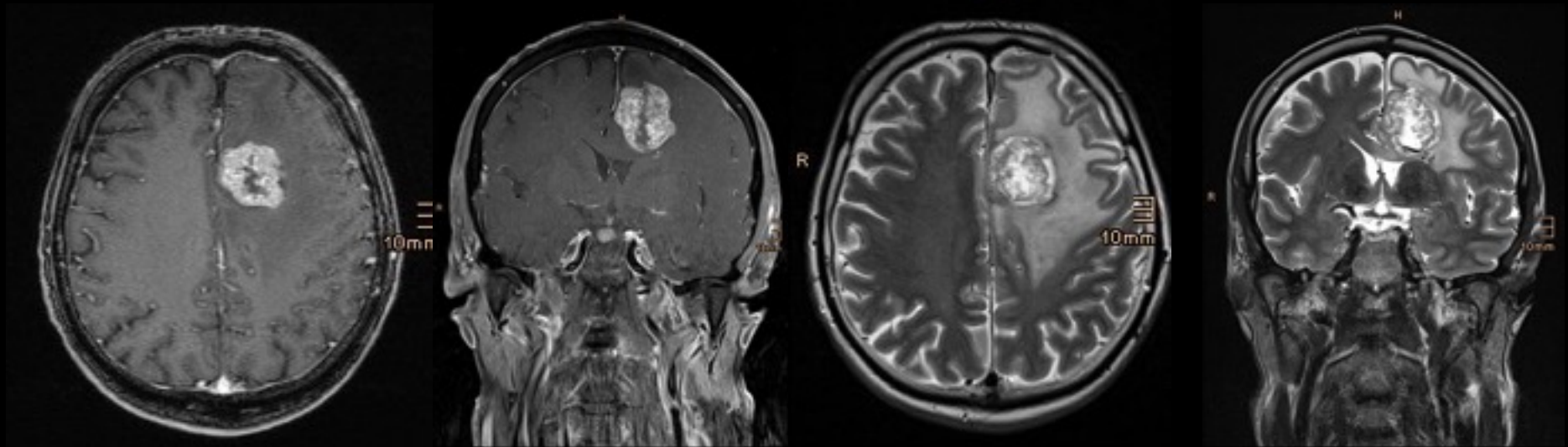
Case 1: 58 years, male



Case 2: 61 years, male



Metastasis of unknown primary



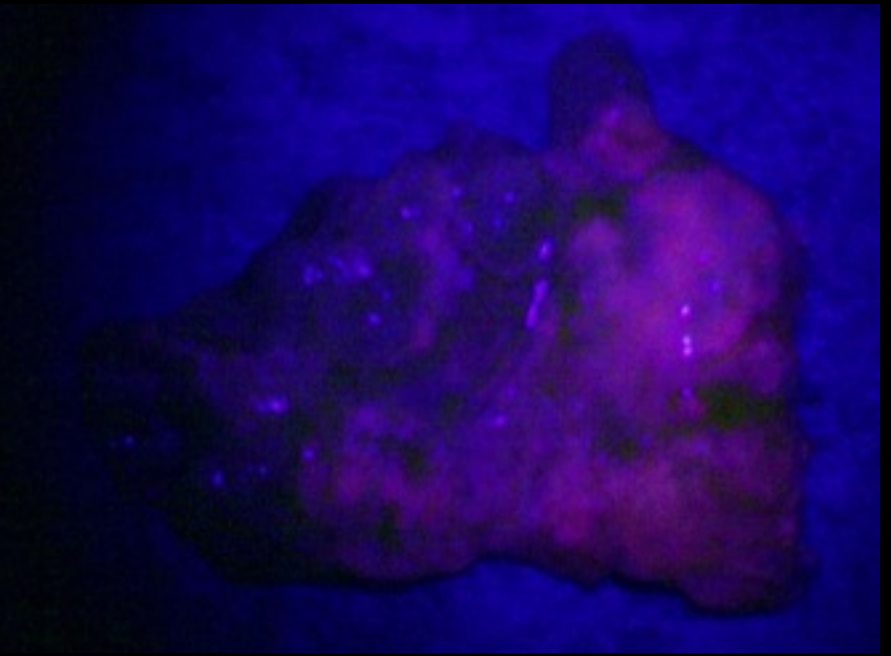
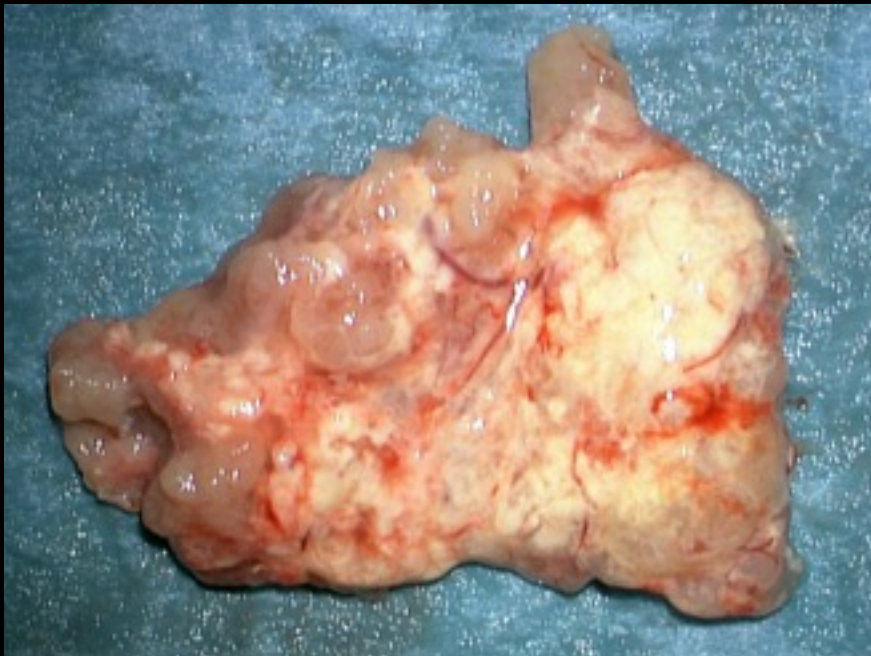
Case 2: 61 years, male



Case 2: 61 years, male



Metastasis showed a heterogenous fluorescence pattern with areas of vague and negative fluorescence



5-ALA in Brain Metastasis Literature

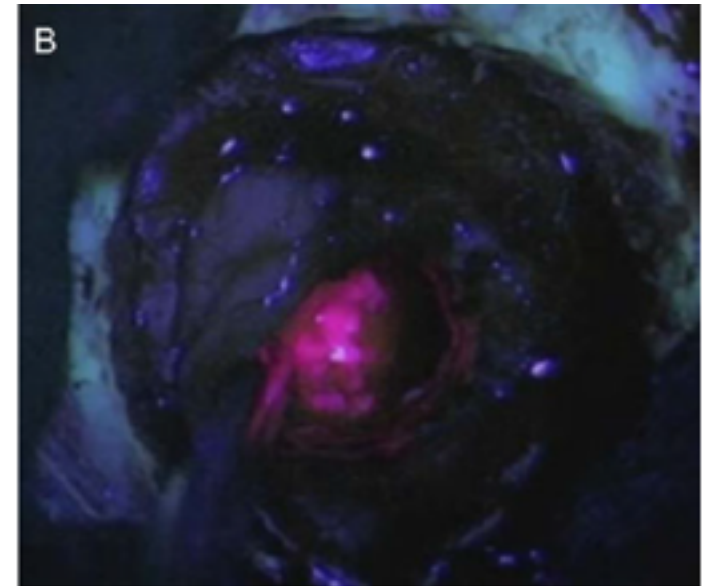


5-Aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study

**Marcel A. Kamp • Philipp Grosser • Jörg Felsberg •
Philipp J. Slotty • Hans-Jakob Steiger •
Guido Reifenberger • Michael Sabel**

Acta Neurochir (2012) 154:223–228

- 62% (32/65) of brain metastases showed 5-ALA induced fluorescence
- Residual tumor tissue was histologically confirmed in 6 of 18 patients (33%) with available tissue specimens from fluorescing resection cavity



5-ALA in Brain Metastasis Literature



Use of fluorescence to guide resection or biopsy of primary brain tumors and brain metastases

Neurosurg Focus 36 (2):E10, 2014

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- In total 34 of 65 (52,3%) brain metastases exhibited 5-ALA fluorescence
- Subgroups like metastasis from SCLC (4/4 patients; 100%) demonstrated an even higher rate of fluorescence

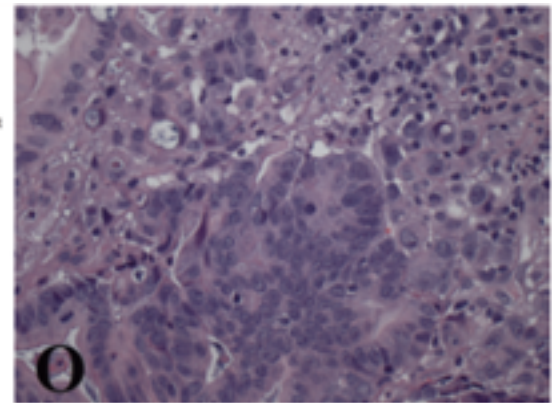
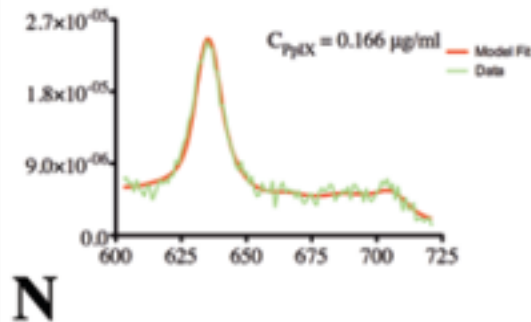
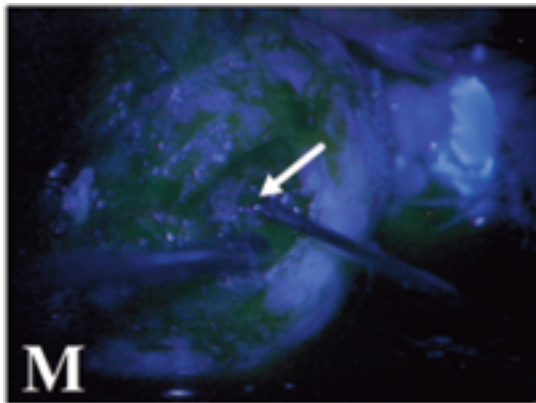
Future steps



- Cooperation with the neurosurgical department in Pölsen/Austria (Prof. Ungersböck/Dr. Marhold) St.
- Histopathological analysis of tumor areas from different fluorescence patterns
- Histopathological analysis of fluorescing surrounding brain tissue, if it can be safely performed in non-eloquent metastases
- Spectroscopic analysis of PpIX accumulation to visualize especially non-fluorescing brain metastases
- Identification of the essential factors of the heme biosynthesis that are responsible for the presence of fluorescence

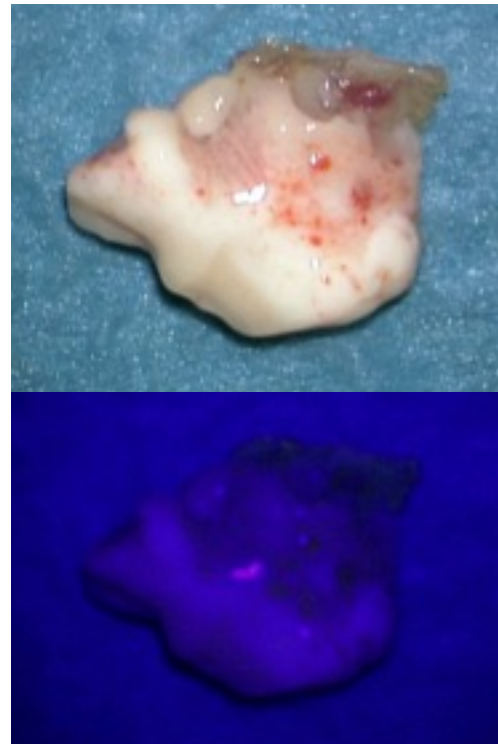
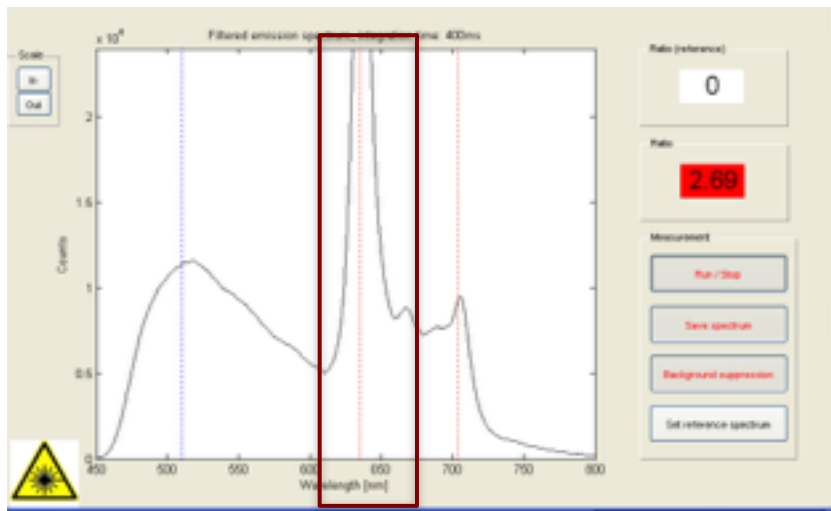
Quantitative spectroscopic analysis of PpIX accumulation

- Spectroscopic probes
- Capable to detect pathological accumulation of PpIX within brain tumors/metastases



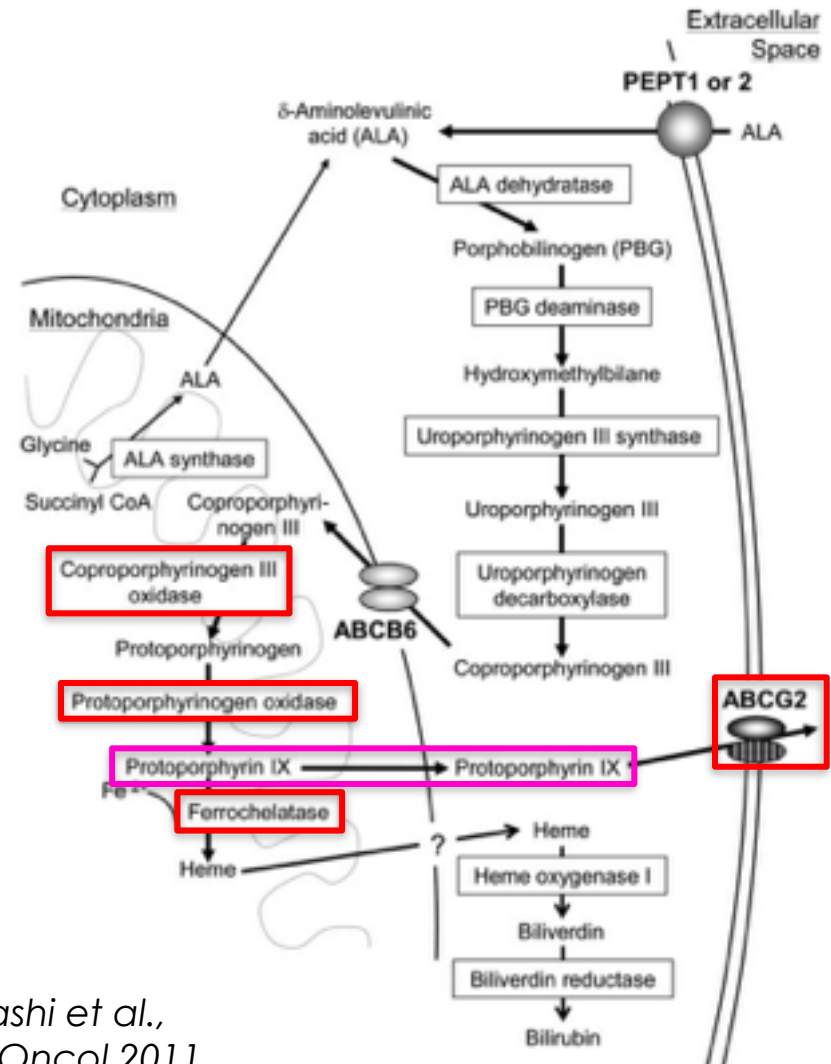
Spectroscopic probe for tissue analysis

Non fluorescing brain metastasis tissue can be identified by spectroscopic analysis



5-ALA and Heme-Biosynthesis

- Identification of the essential factors of the heme biosynthesis
- responsible for the presence or absence of 5-ALA fluorescence
- Potential improvement of the 5-ALA effect for photodynamic diagnosis especially in brain metastasis with no or only vague fluorescence



Takahashi et al.,
Neuro Oncol 2011

Conclusions

5-ALA in Brain Metastases



- In the largest patient series to date, we found visible 5-ALA induced fluorescence in approximately half of the patients.
- Metastases from specific primary tumors (e.g. renal cell cancer) demonstrate particular high rates of visible fluorescence.
- In future, fluorescence-guided surgery of fluorescing metastases might lead to more „radical resections“ to reduce the rate of recurrence.
- The significance of fluorescing surrounding brain tissue (66% of cases) and its impact on recurrence has to be clarified in further studies.
- Typical fluorescence patterns of brain metastases facilitate intraoperative tumor differential diagnosis.



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