

# Fluorescence-guided brain tumor surgery (FGS) and intraoperative monitoring of Protoporphyrin IX (PPIX) using ALA (Gleolan™)

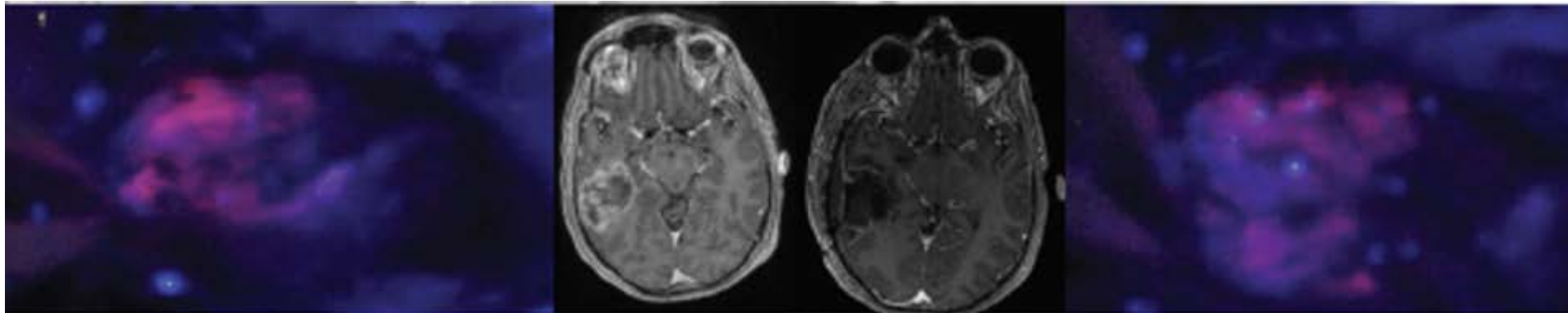
ICD-10 Coordination and Maintenance Committee Meeting  
Centers for Medicare & Medicaid Services

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# Fluorescence-Guided Surgery (FGS) Using Gleolan™ (aminolevulinic acid HCl)

- Gleolan™ (ALA) was recently approved as an Orphan Drug by FDA as the first FGS agent available to neurosurgeons
- Indicated in patients with glioma (suspected World Health Organization Grades III or IV on preoperative imaging) as an adjunct for the visualization of malignant tissue during brain surgery
- The drug is reconstituted in the hospital pharmacy based on weight-based volume and administered orally 3 hours prior to surgery under the supervision of a healthcare professional while the patient is monitored for hypersensitivity in a dimly lit environment
- ALA is converted by the body into Protoporphyrin IX (PPIX)
- When illuminated under blue light with special filters, the PPIX in the tumor glows an intense red-violet, while the normal brain tissue appears blue



# Background on Gliomas

- Types of brain tumors
  - Primary (including high grade gliomas originating in the brain)
  - Secondary (metastasis from other tumor sites)
- Incidence/Prevalence ~50,000 per year
  - Primary brain tumors are categorized by WHO (Grade III/IV lethal malignancies)
    - High Grade III-IV Gliomas are rare – affecting ~12,000 annually in the US
    - Low Grade I-II Gliomas (affecting ~40,000 annually) are poorly defined by pre-operative imaging with 40% hiding undefined regions of high grade tumor
  - Distribution: Men and women equally impacted, predominantly > 50 years of age
- Standard of Care: Surgery / Radiation and chemotherapy
- Prognosis: Median survival 13 months

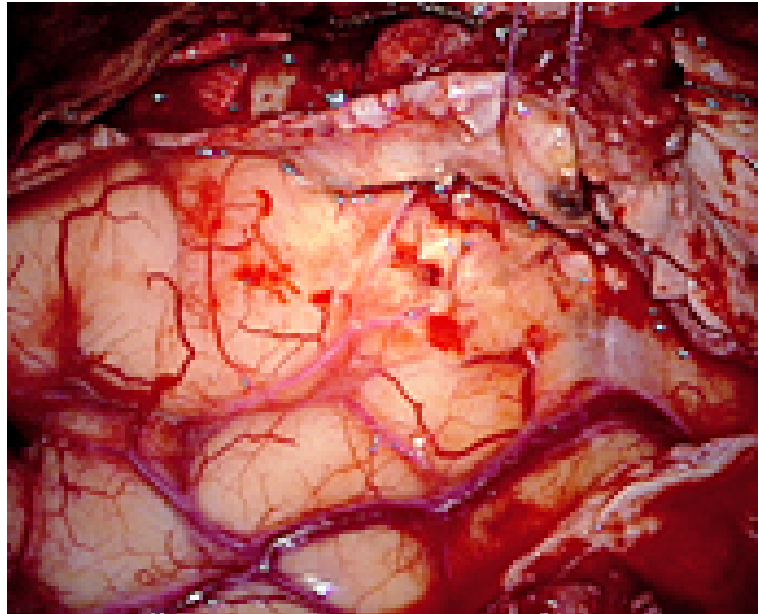
# What Does Fluorescence-Guided Surgery (FGS) Do?

Real-time tumor visualization with ALA (Gleolan) improves localization of suspected high-grade (Grades III or IV) malignant brain tumors

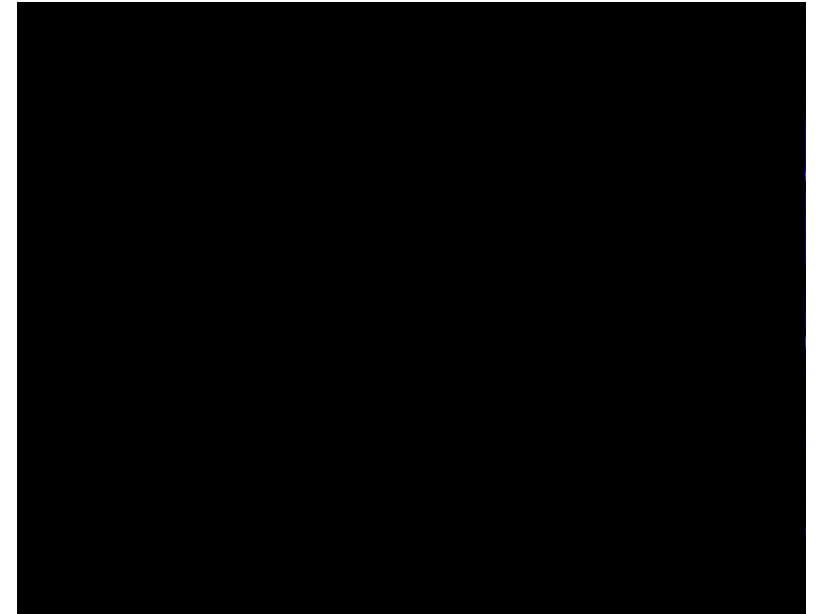
**Glioma Tumor Cell**



**High Grade Glioma Under  
White Light**



**High Grade Glioma Using  
Gleolan Under Blue Light**



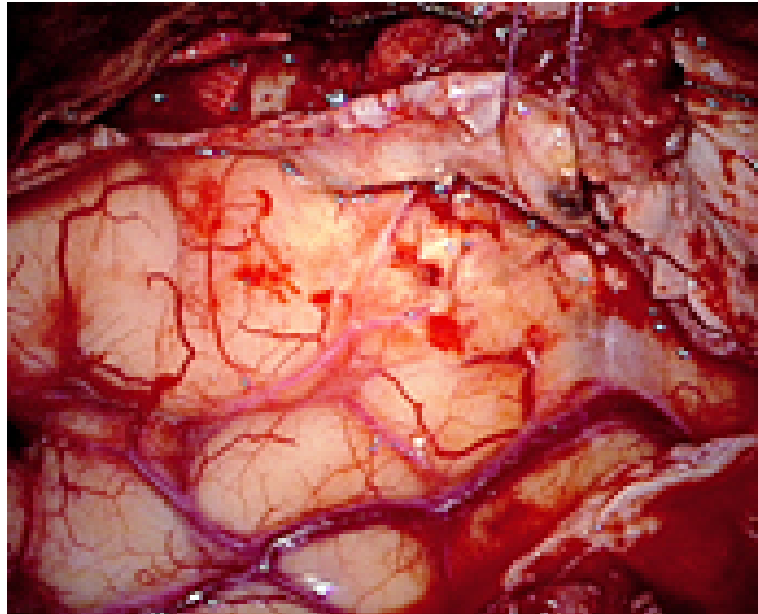
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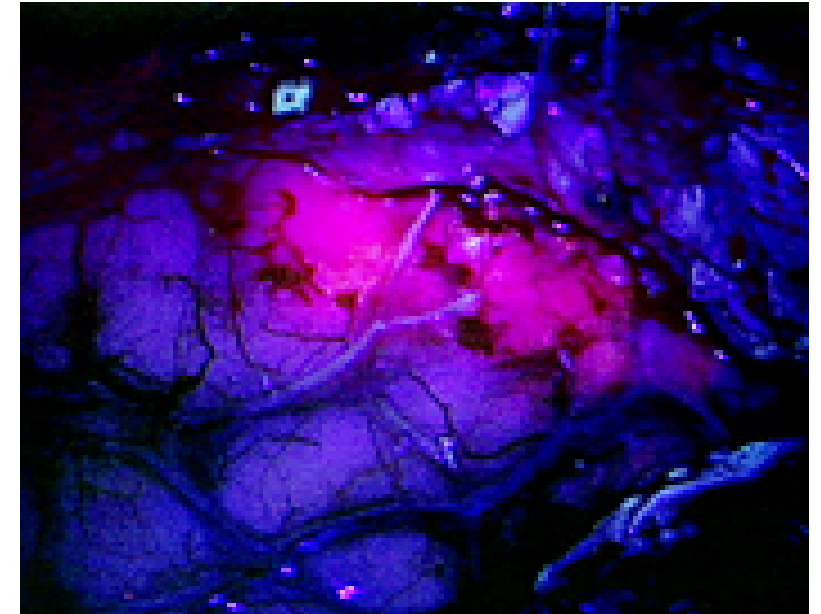
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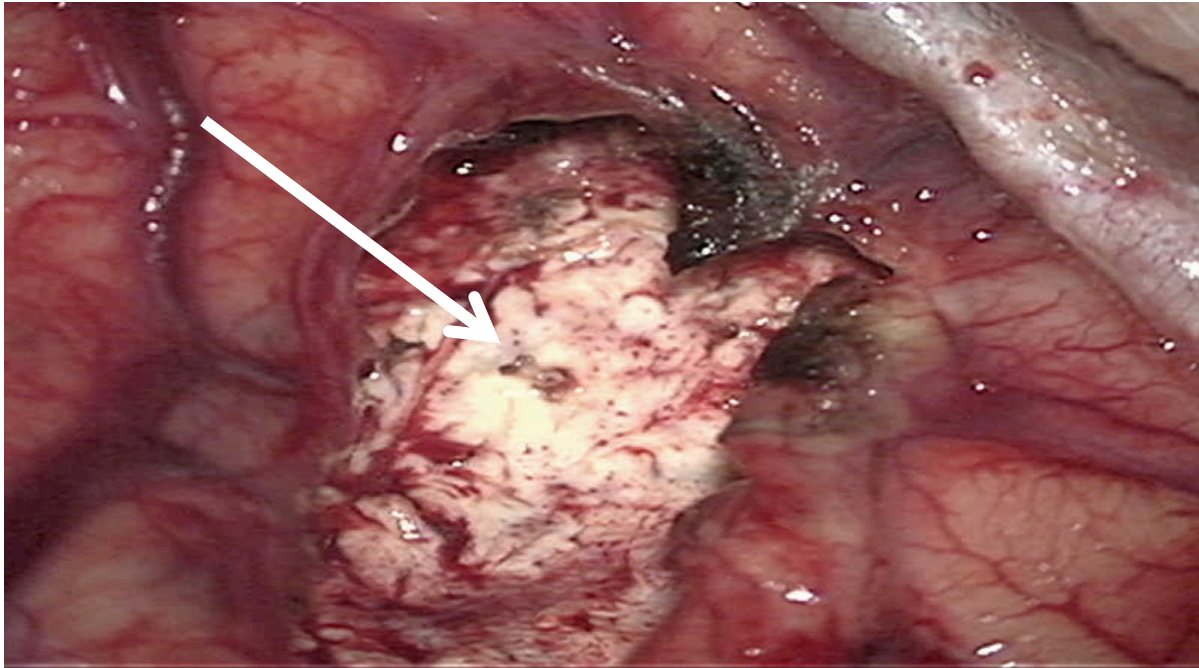


# FGS Offers New Approaches to Immediately See Brain Tumors Never Seen Before



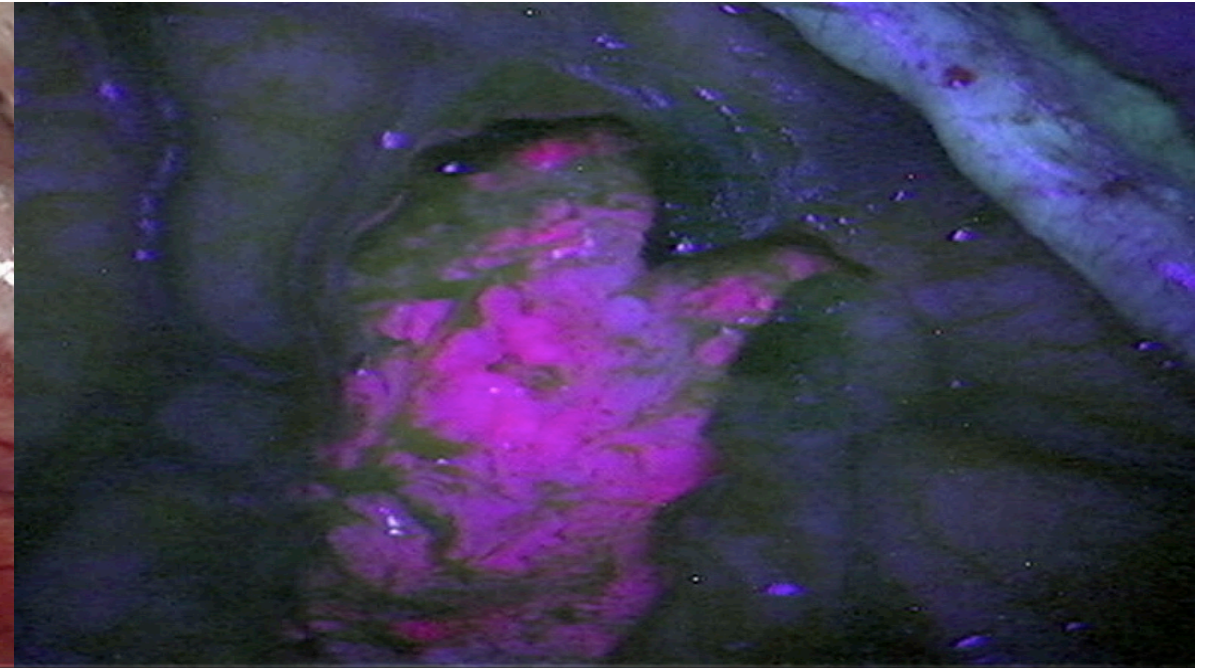


# Most Glioma Tumor Resection Surgeries Performed Under White Light Fail to Adequately Remove the Brain Tumor



## **White Light illumination**

Normal appearing brain after maximal resection; **End of Surgery**



## **Gleolan illumination**

Red-violet fluorescence is Highly Predictive of Tumor Presence to improve tumor removal

# Limitations of Brain Tumor Surgery without Fluorescent Imaging

- 66% of brain tumor surgeries leave unseen tumor ( $>1\text{ cm}^3$ ) and poor outcomes
- Tumor margins extremely difficult to assess using traditional white light
- 'Brain shift' and poor visualization limit current use of procedures such as iMRI and navigation
- Suboptimal resection results in early recurrence and decreased survival
- If total resection is achieved, length of survival increases dramatically and need for intervention is reduced

***With 50% mortality at Year 1 and 70% at Year 2,  
surgeons are seeking a better way to see and remove malignant brain tissue***



# Tumor Resection Surgery

For procedures without FGS with ALA (Gleolan), dictation may include the following terminology:

## Pre-operative Preparation

- Preoperative preparation
- Dx and workup
- MRI
- Possible biopsy
- Surgical planning and pre-op care

## Surgical Procedure

- Anesthesia (exception - awake craniotomy)
- Incision through scalp/ craniotomy
- Bone and brain covering removed to access tumor
- Neuronavigation to locate tumor
- Potential use of adjunctive tools such as Intraoperative MRI\* and electrical mapping to avoid regions of vital function
- Introduction of surgical microscope to magnify tumor and co-registration with GPS type software
- Tumor location subject to misinformation due to brain shift
- Resection to limits of MRI defined edge location guided by best practice
- Wound repair, end of case
- Post-op care



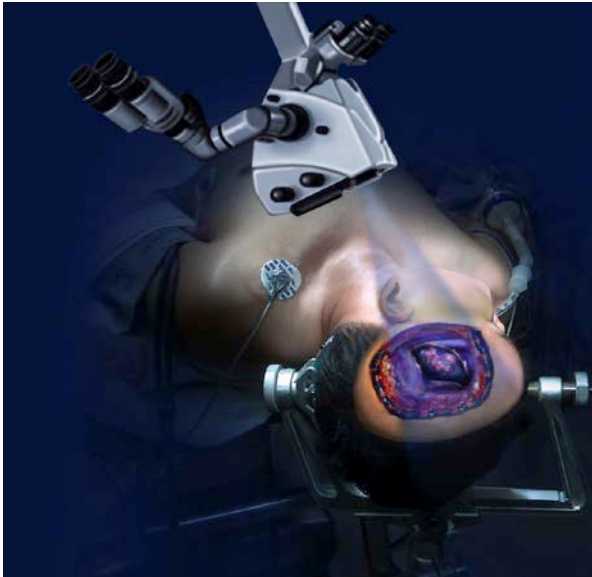
\*Few institutions (~40) utilize intraoperative MRI

# Tumor Resection Surgery with Fluorescence-Guided Surgery

For procedures without FGS with ALA (Gleolan), dictation may include the following terminology:

## Pre-operative Preparation

- Preoperative preparation
- Dx and workup
- MRI
- Possible biopsy
- Surgical planning and pre-op care
- **Reconstitution of Gleolan <24 hrs**
- **Administration of Gleolan 3 hrs before surgery**

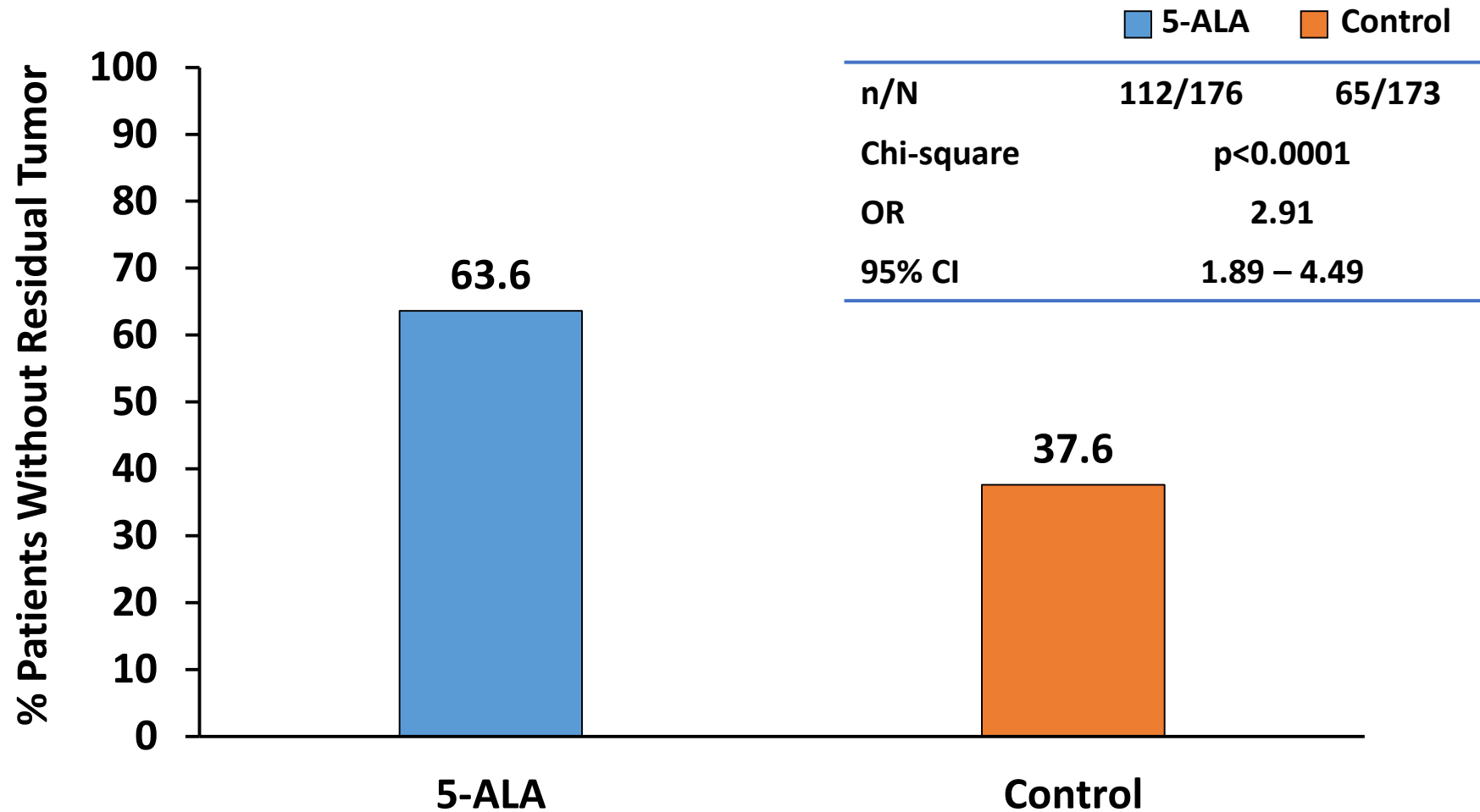


## Surgical Procedure

- Anesthesia (exception - awake craniotomy)
- Incision through scalp/ craniotomy
- Bone and brain covering removed to access tumor
- Neuronavigation to locate tumor
- Potential use of adjunctive tools such as Intraoperative MRI\* and electrical mapping to avoid regions of vital function
- Introduction of surgical microscope to magnify tumor and co-registration with GPS type software
- **Tumor removal to maximal extent under white light**
- **Blue filter placed on white light to activate PPIX (red-violet immediately observed) defining tumor location no longer subject to misinformation due to brain shift**
- **Resection to limits beyond MRI defined edge location guided by real time fluorescence, and surgery continues until all that can be removed safely is removed. Elective biopsies conducted.**
- Wound repair, end of case
- Post op care

\*Few institutions (~40) utilize intraoperative MRI

# Fluorescence Guided Surgery Improves Tumor Visualization and Removal

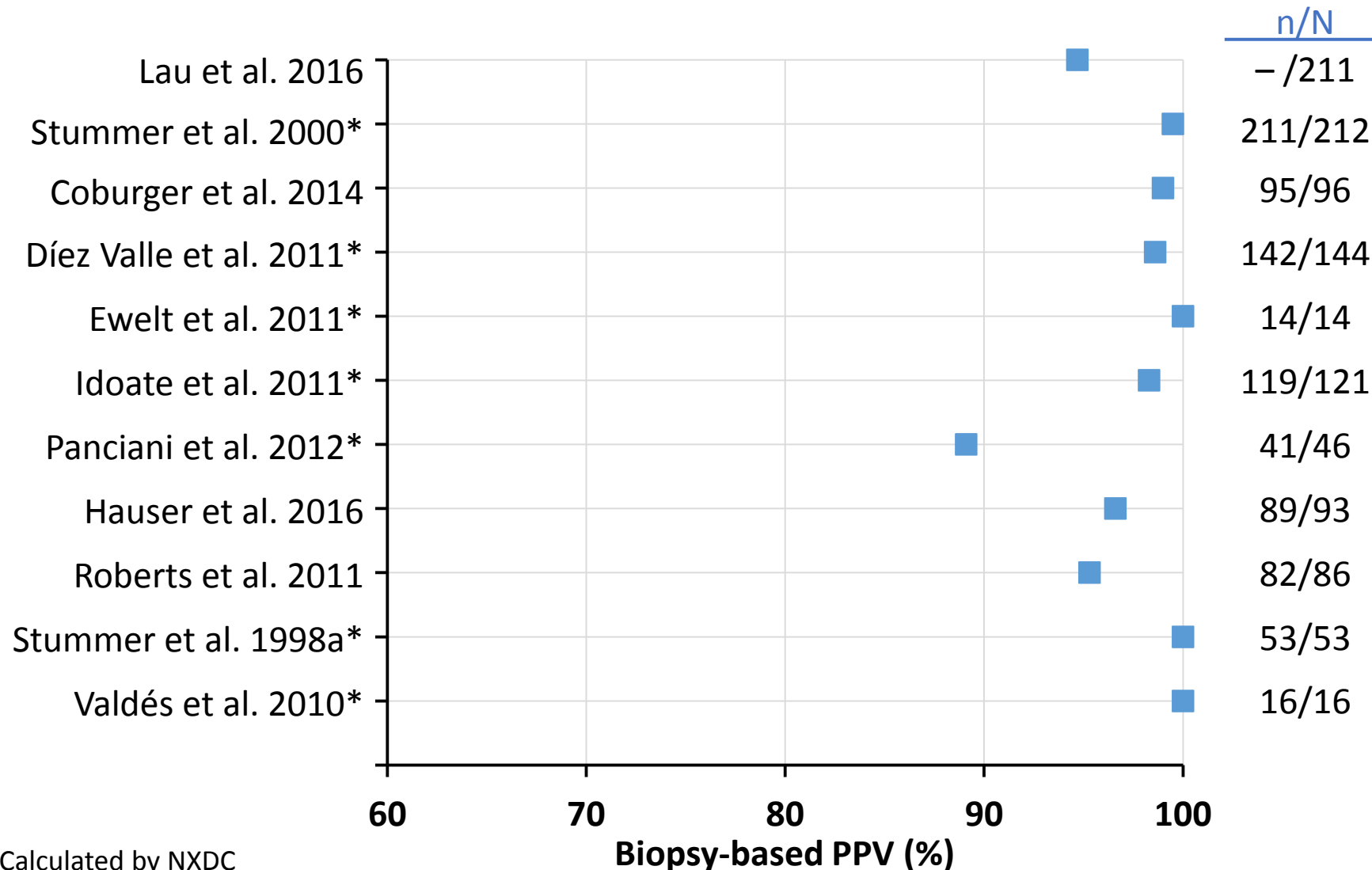


# Totality of Evidence Confirms Clinical Benefit of Gleolan

- Clinical trial data (6 sponsored studies, FDA approved)
- Peer review publications (> 40 with several meta-analysis)
- Standard of care to use Gleolan in Europe

	Numbers of Patients		
	Six Sponsored Studies	Scientific Literature	Global experience
Efficacy	418	377	–
Safety	527	≈2,000	≈58,000

# Positive Predictive Value as Published in Peer-Reviewed Literature



# Summary of Efficacy and Clinical Benefits

- **Predictive accuracy**
  - Fluorescence highly predictive of malignant tumor (PPV ~95%)
- **Clinical usefulness**
  - Additional malignant tumor visualized with Gleolan FGS
  - Demonstrated use of FGS for enhancing delineation of tumor: High Positive Predictive Value
  - Ability to aid surgeons in identification of malignant tumor under fluorescent light that may otherwise be overlooked during conventional microsurgical resection
  - Improved visualization is important to the surgeon and patient to ensure best practice in approaching tumor burden
- **Clinical significance**
  - Significantly more patients with maximal tumor removal (63.6 vs 37.6%)
  - Significant improvement in Progression Free Survival
  - Post-hoc analysis suggests reduced need for subsequent surgeries
  - Data from literature consistent with pivotal studies



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