

Neuro Oncology: Novel Advances in Therapy

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Surround yourself with good friends:

- **JASON BOURNE**
- **JACK REACHER**
- **JOHN WICK**
- **JACK RYAN**
- **ETHAN HUNT (The Impossible Mission Force)**
- **TONY STARK (The Avengers)**

Quotes of the Mission: Impossible Franchise





Ethan Hunt, Mission: Impossible - Dead Reckoning Part One

"A Nuclear Bomb is Something You Bother Me with Immediately"



William Brandt, Mission: Impossible - Rogue Nation

**"I Can Neither Confirm Nor Deny Details Of Any
Operation..."**



Ethan Hunt, Mission: Impossible - Rogue Nation

"Not 'In' the Plane, 'On' the Plane"



Ethan Hunt, Mission: Impossible - Fallout

"I Am the Storm"

The Warrior...

- **Fate whispers to the warrior - you will not withstand the storm - the warrior whispers back - I am the storm**

Overview

Presentation title



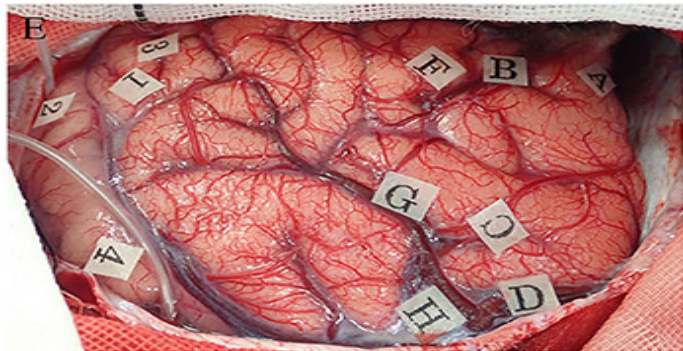
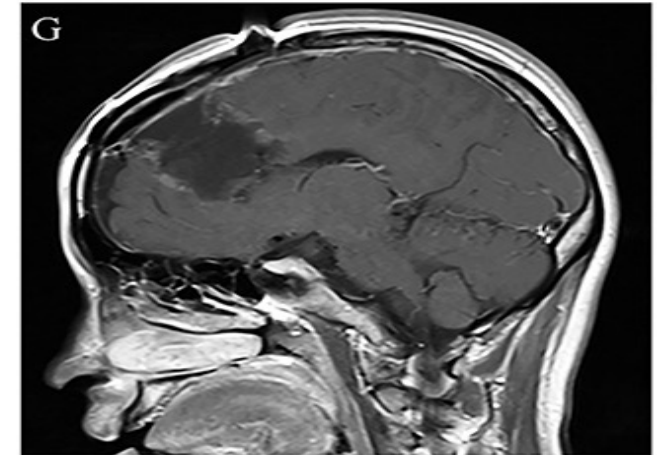
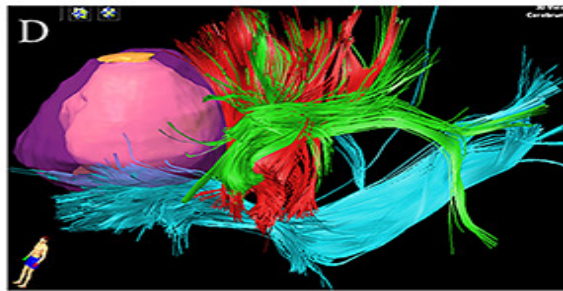
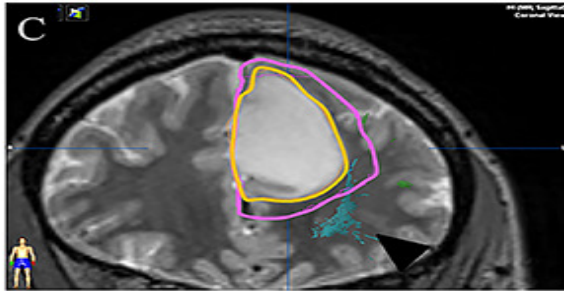
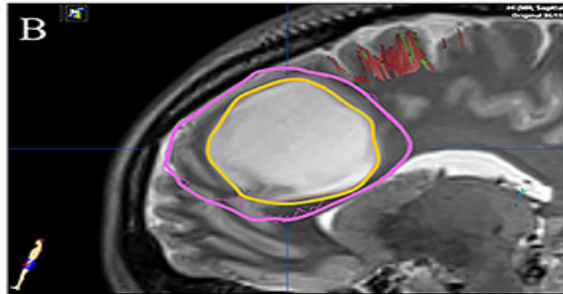
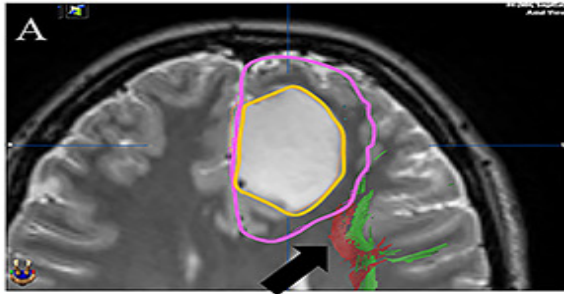
- **INTRODUCTION**
- **MOLECULAR PATHOLOGY**
- **CLINICAL TRIALS**
- **TREATMENT PARADIGMS**

Surgical Option:

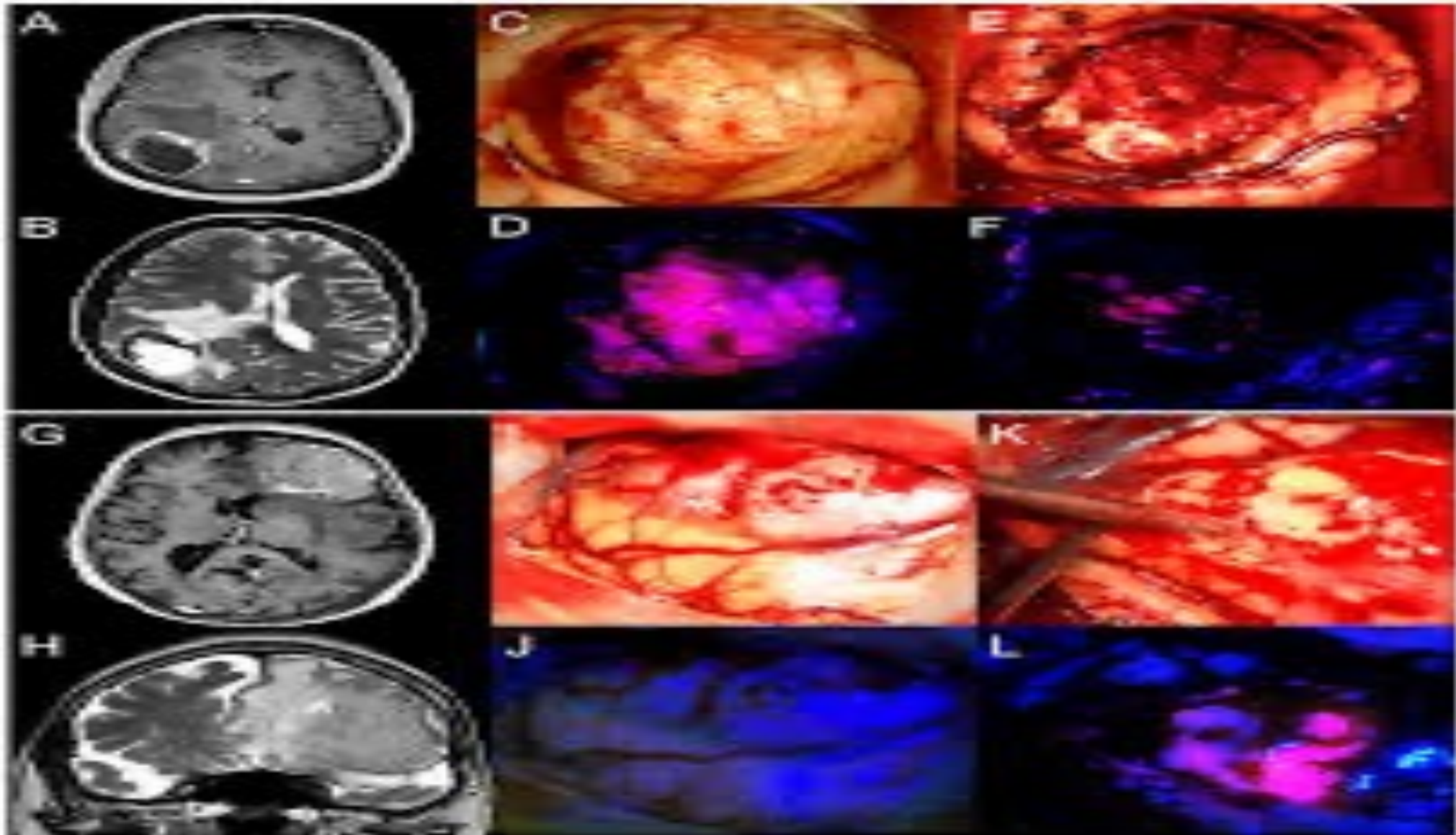
Surgical Planning:

- **Maximal Safe Surgical Resection**
- **Supra - Maximal Resection**
- **Fluorescence Guided Surgery / 5 ALA**
- **Connectomics / Fiber Tracking**
- **Intra - Operative MRI**
- **Awake Craniotomy**

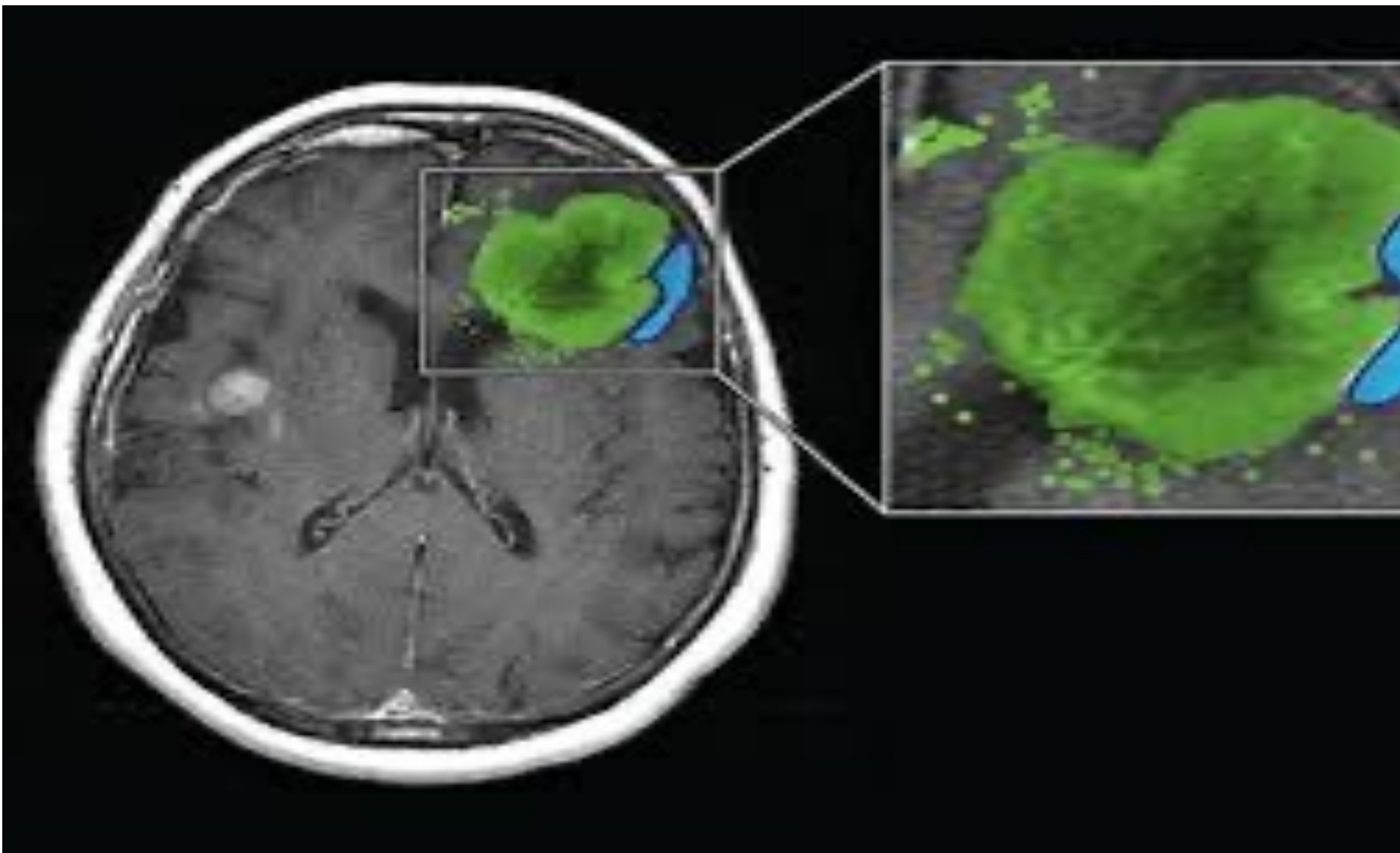
Supra - Maximal Resection:



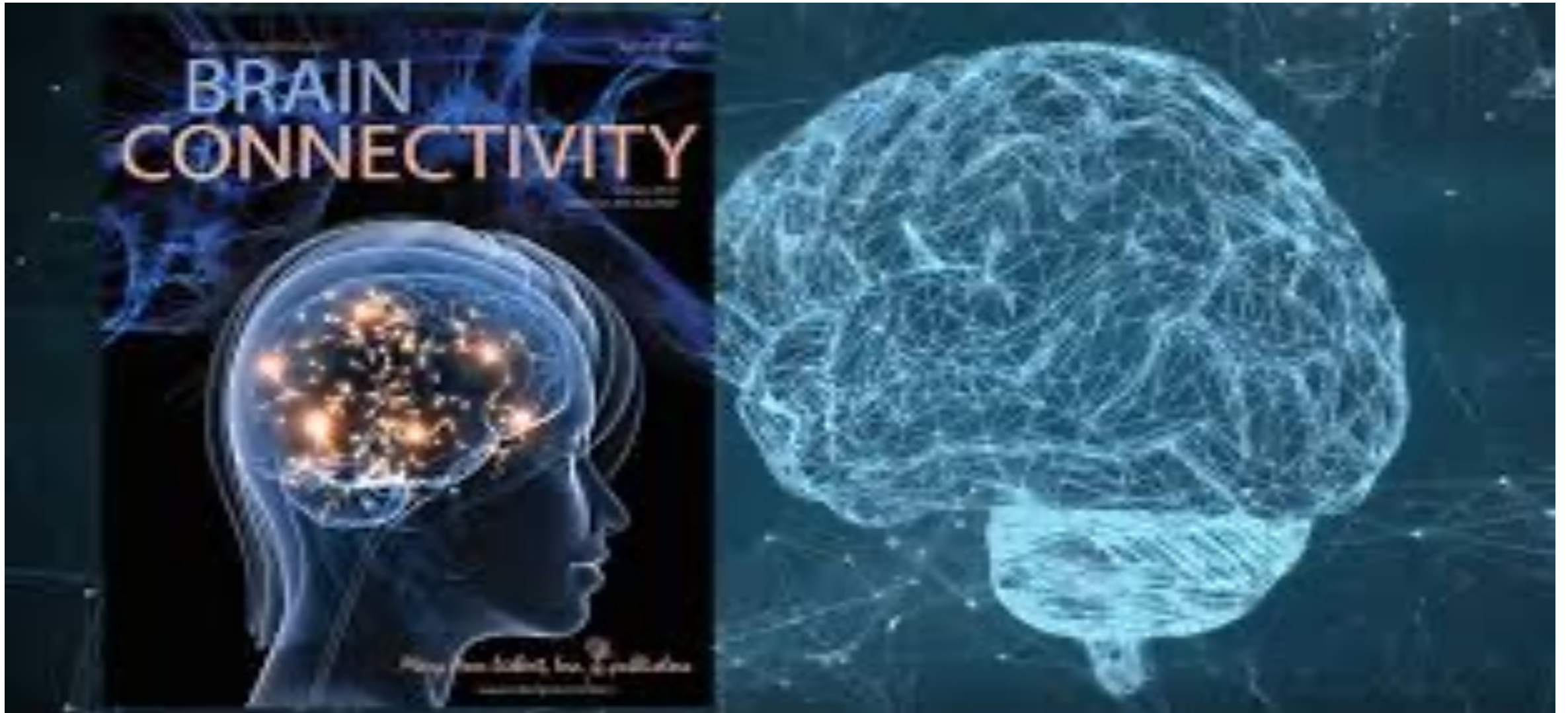
Fluorescence Guided Surgery:



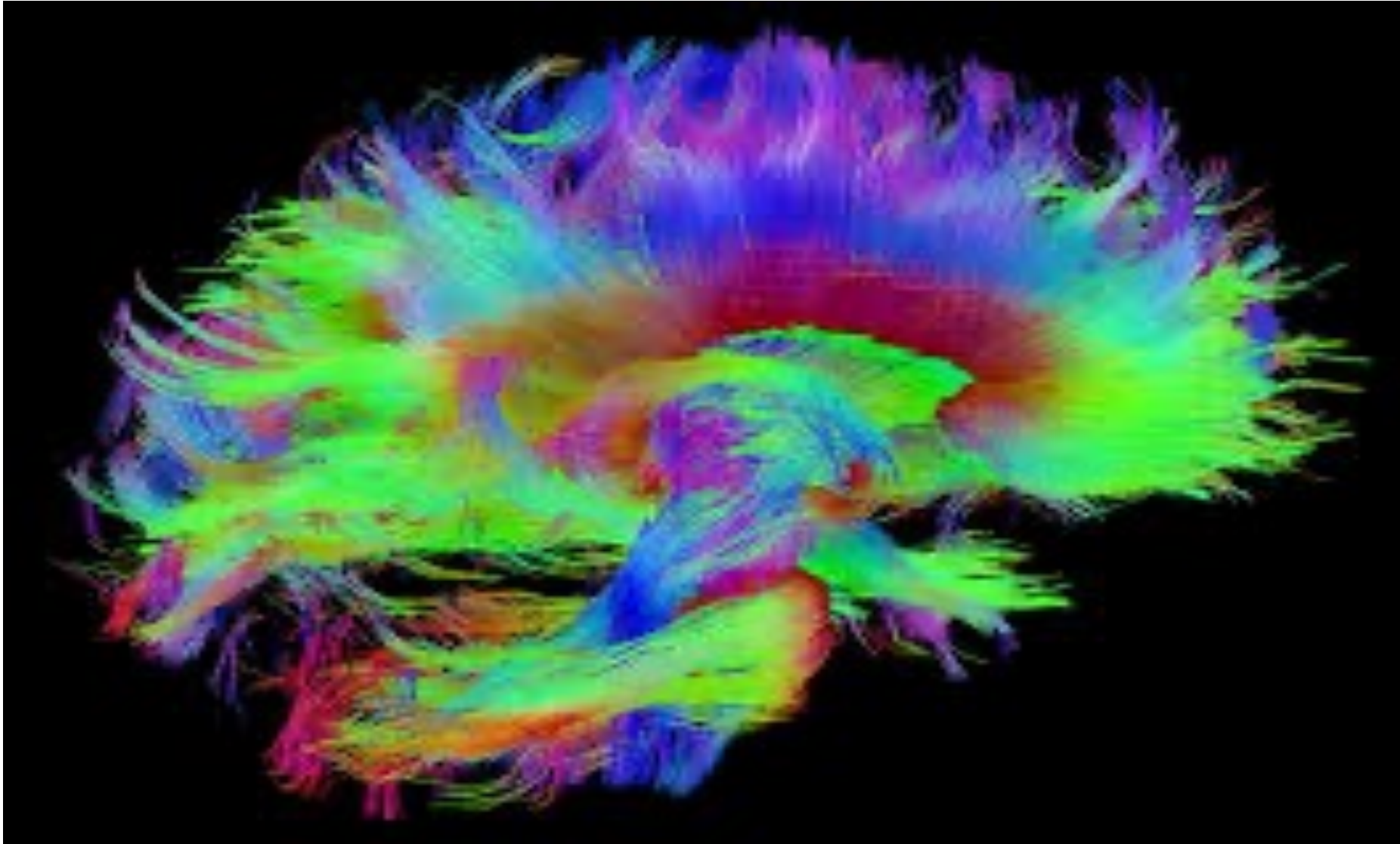
Fluorescence Guided Surgery:



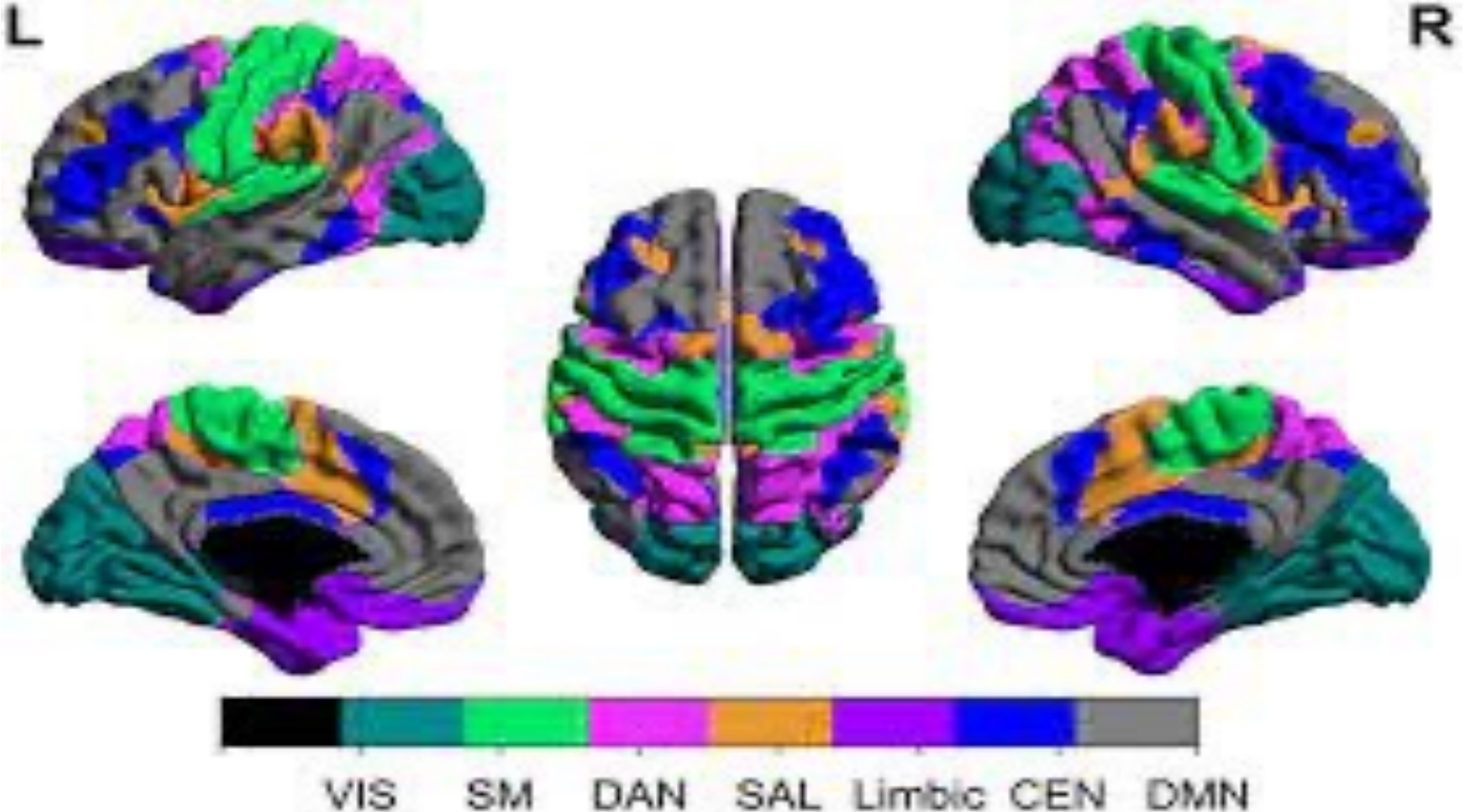
The Brain Connectome:



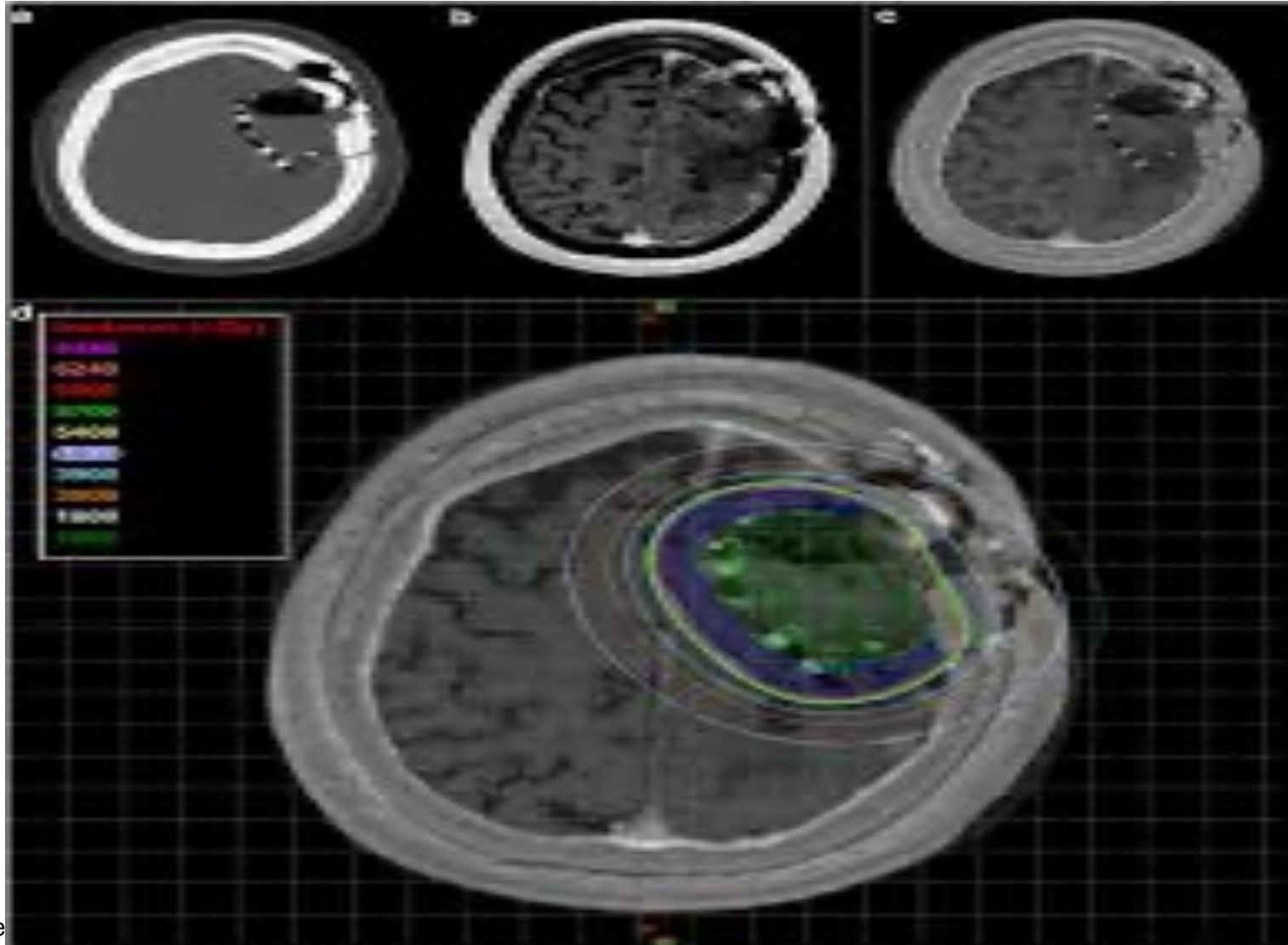
The Human Connectome Project:



The Brain Connectome:



Intra - Cavitory Brachytherapy:



New GBM: "Gestalt Trial" GTM 103

- **Cesium 131 Radioactive Seeds** embedded in an absorbable collagen matrix
- **Brachytherapy in the surgical cavity of GBM** followed by reduced dose IMRT + TMZ

CNS Metastasis: GTM 102

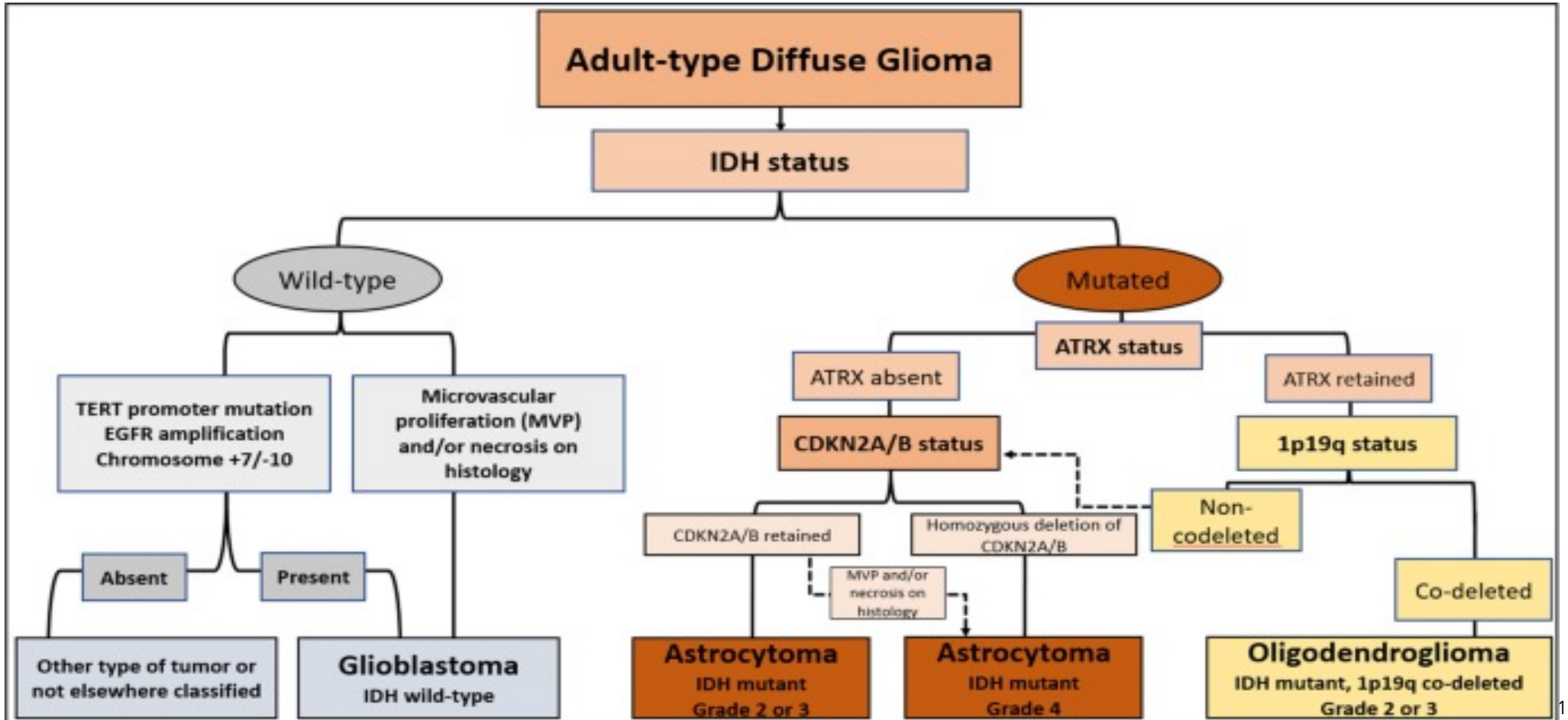
- **"ROADS TRIAL"**
- **Resectable CNS Metastasis**
- **50 / 50 Randomization between Resection + Cesium 131 Brachytherapy VS Resection + SRS**



Ethan Hunt, Mission: Impossible - Dead Reckoning Part One

"We Live And Die In The Shadows..."

Glioma Molecular Pathology:



Radiotherapy:

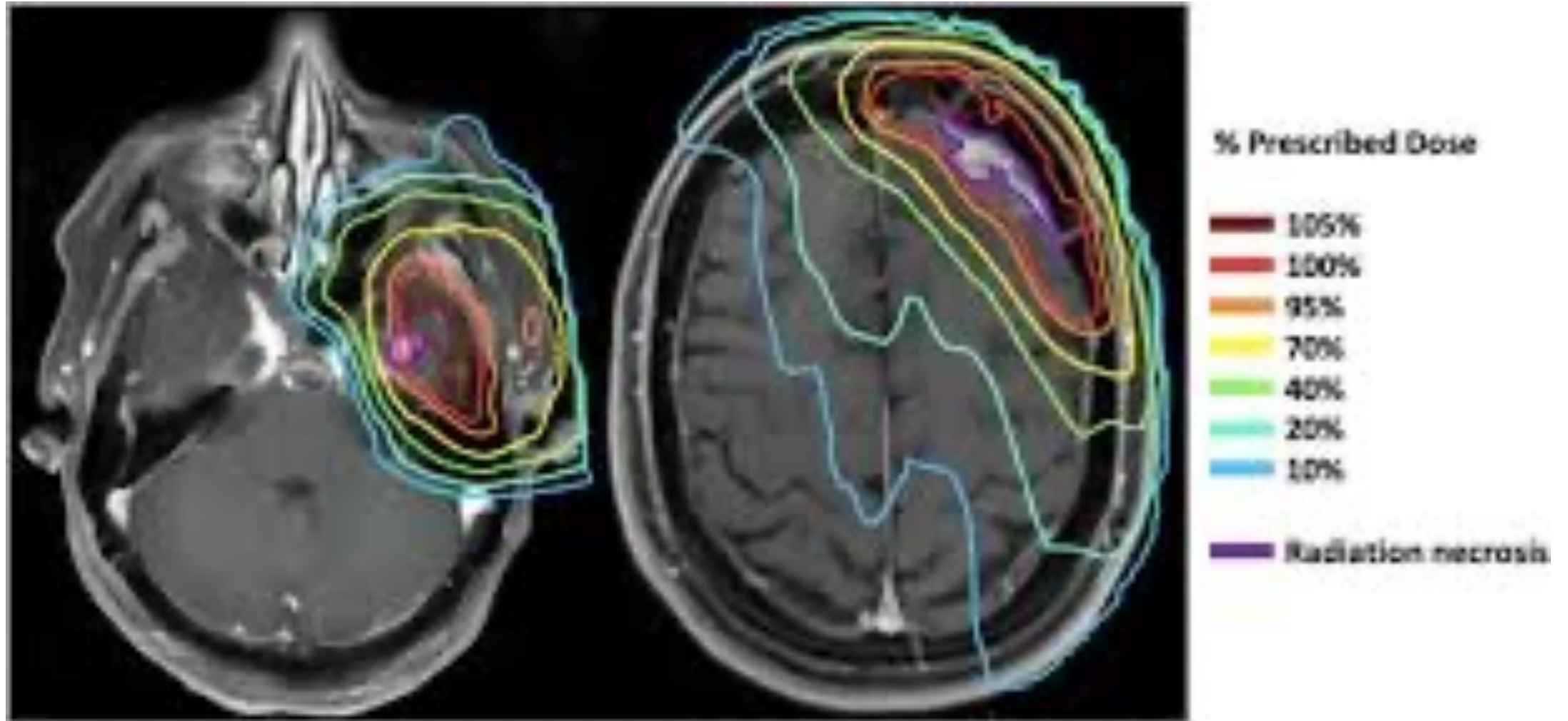
Photon Based RT

- **IMRT**
- **SRS / SRT**
- **Intracavitary Brachytherapy**

Proton Based RT

- **IMPT**

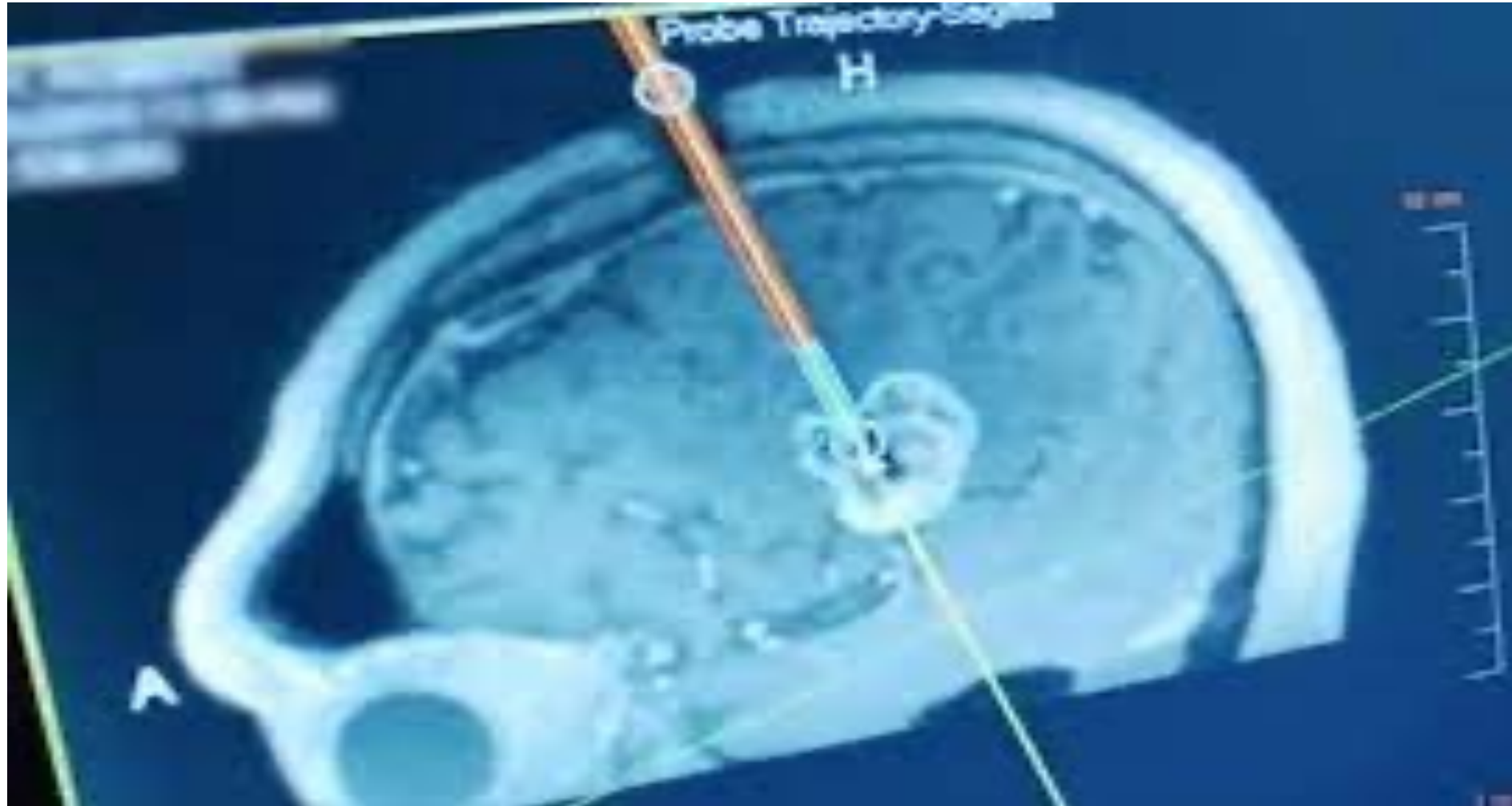
Proton vs Photon RT:



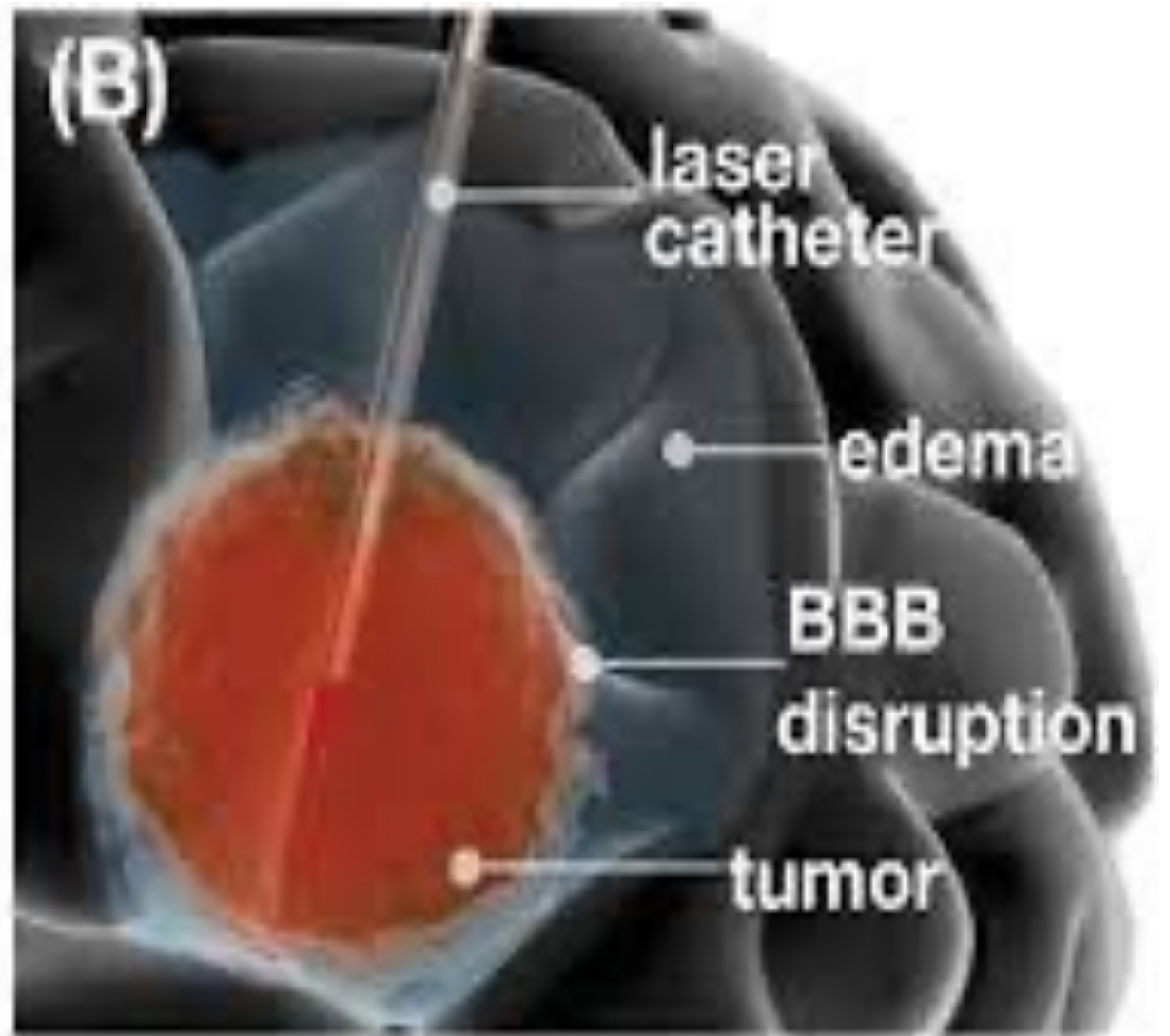
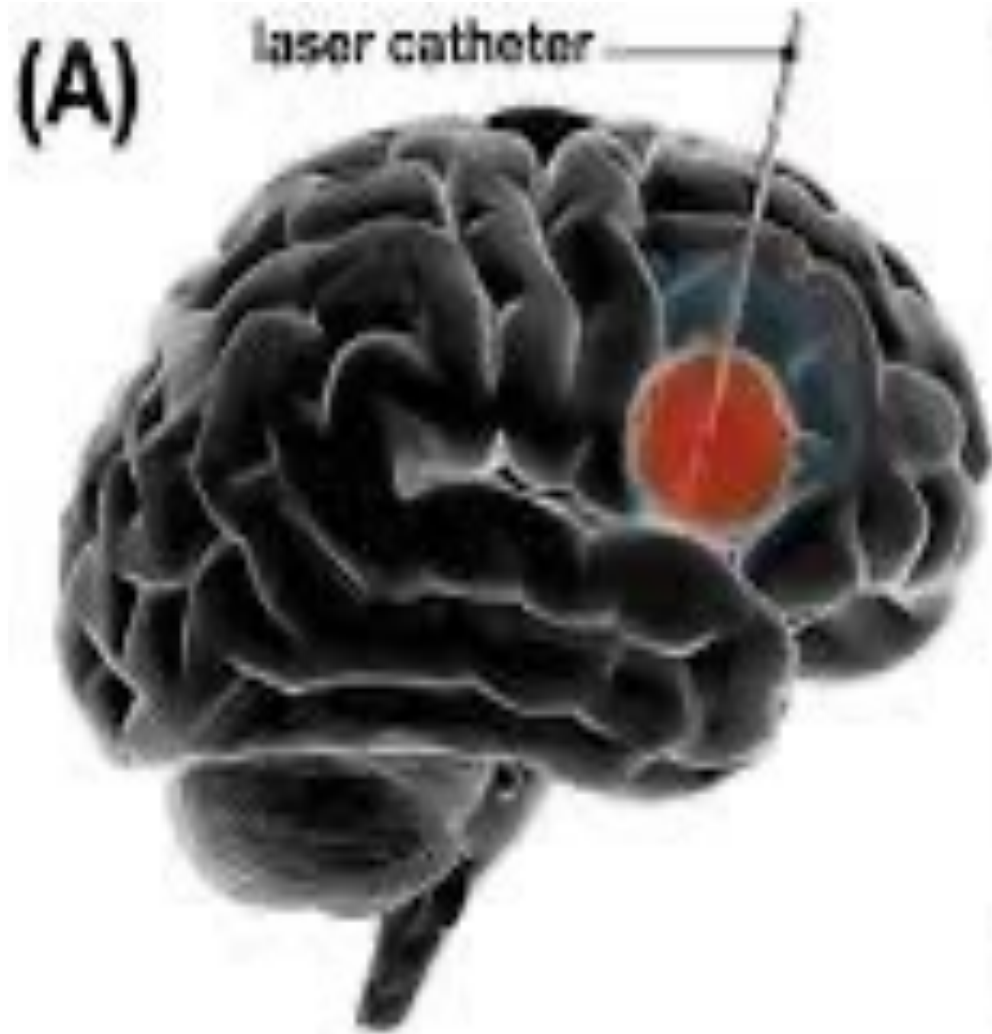
Proton therapy

Photon therapy

Laser Interstitial Thermal Therapy:



Laser Interstitial Thermal Therapy:





Alan Hunley, Mission: Impossible - Rogue Nation

"We Need Reliable Intelligence, And We Need It Now..."

Challenges in Glioma Management:

- **Tumor Heterogeneity**
- **Driver Mutations**
- **Intra-tumoral Genomic Heterogeneity**
- **Inter-tumoral Genomic Heterogeneity**
- **Temporal Genomic Heterogeneity**
- **Immunologically Cold Tumors**
- **Drug Target Engagement**
- **Blood Brain Barrier Challenge**

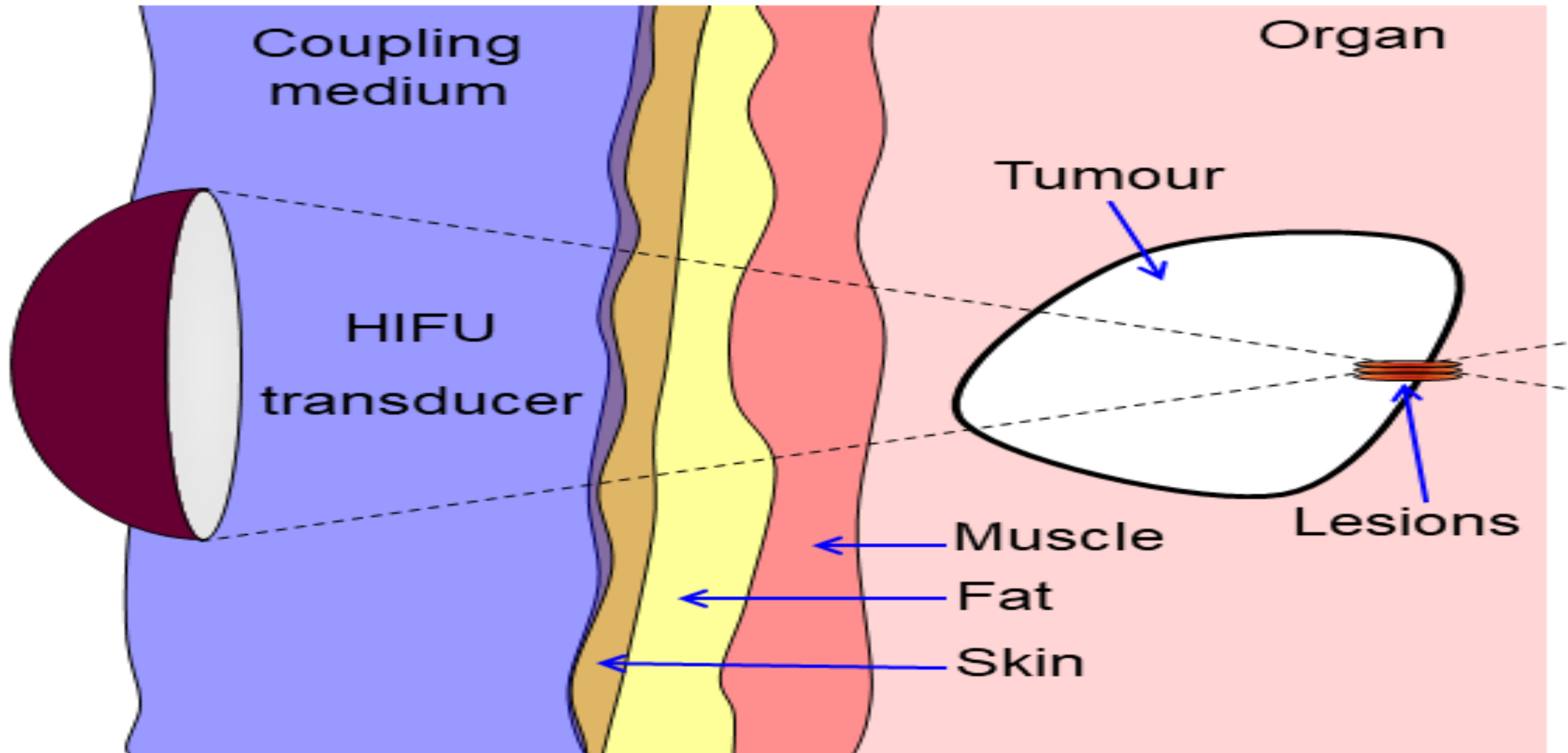
High Intensity Focused Ultrasound:



Presentation title

20XX

High Intensity Focused Ultrasound:



Next Generation Clinical Trials:

NRG TRIALS

ALLIANCE TRIALS

BRACHYTHERAPY TRIALS

NRG BN 005:

- **A Phase II Randomized Trial of Proton vs. Photon Therapy (IMRT) for Cognitive Preservation in Patients with IDH Mutant, Low to Intermediate Grade Gliomas**
- **Open to accrual**

NRG BN 010:

- **A Safety Run-In and Phase II Study Evaluating the Efficacy, Safety, and Impact on the Tumor Microenvironment of the Combination of Tocilizumab, Atezolizumab, and Fractionated Stereotactic Radiotherapy in Recurrent Glioblastoma**
- **Open to accrual**

NRG BN 012:

- **A Randomized Phase III Trial Of Pre-Operative Compared To Post-Operative Stereotactic Radiosurgery In Patients With Resectable Brain Metastases**
- **? Reduction in the risk of Leptomeningeal Metastasis with Pre-Op SRS followed by resection**

IDH 1 / IDH 2 Mutated Glioma:

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Mellinghoff IK et al. DOI: 10.1056/NEJMoa2304194

CLINICAL PROBLEM

Gliomas, the most common malignant primary brain tumor type in adults, are categorized by histologic and molecular features and by tumor grade. Almost all grade 2 gliomas have mutations in the genes encoding the metabolic enzymes isocitrate dehydrogenase 1 (IDH1) or 2 (IDH2).

CLINICAL TRIAL

Design: This phase 3, double-blind, randomized, placebo-controlled trial tested the clinical effects of vorasidenib — an oral brain-penetrant inhibitor of mutant IDH1 and IDH2 enzymes — in patients with residual or recurrent grade 2 IDH-mutant glioma who had undergone surgery as their only previous treatment.

Intervention: 331 patients were assigned to receive oral vorasidenib (40 mg once daily) or matched placebo in 28-day cycles. The primary end point was imaging-based progression-free survival.

RESULTS

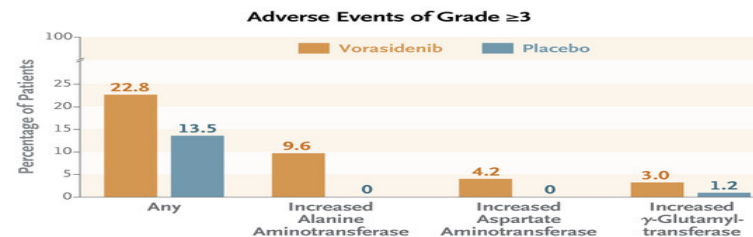
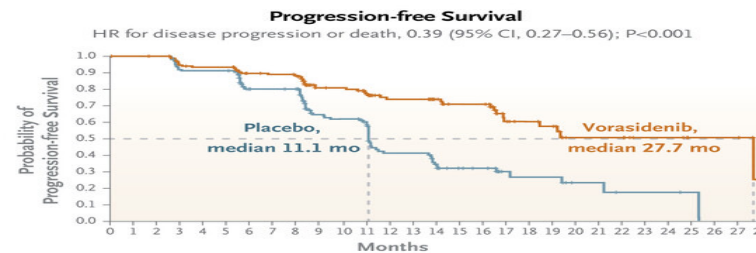
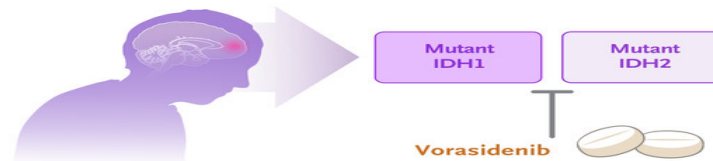
Efficacy: Progression-free survival was significantly longer with vorasidenib than with placebo.

Safety: Although most adverse events with vorasidenib were mild, events of grade ≥ 3 were more frequent with vorasidenib than with placebo; the most common was an increase in alanine aminotransferase level. Serious adverse events that were determined by the investigators to be related to the trial drug or placebo occurred in 1.8% of vorasidenib recipients and in no placebo recipients.

LIMITATIONS AND REMAINING QUESTIONS

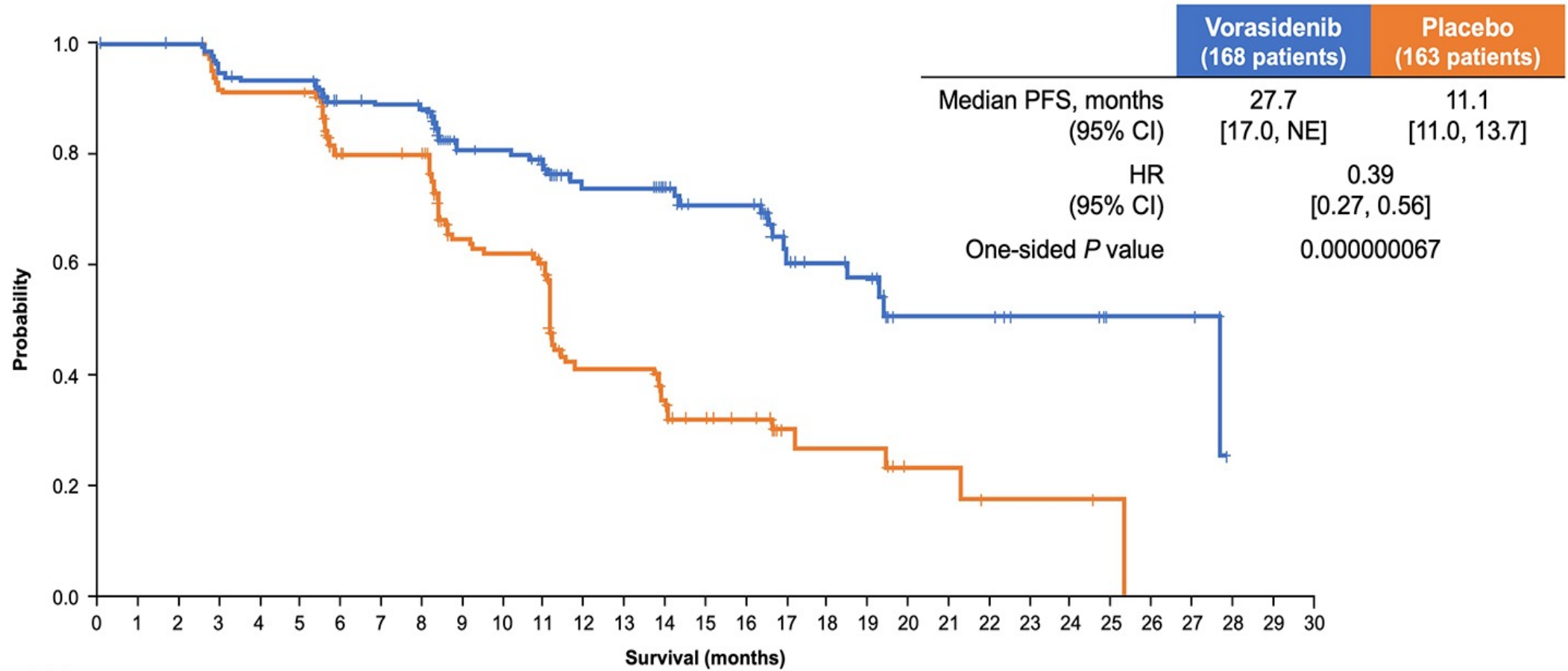
- Patients with high-risk features were excluded from the trial.
- Additional end points, including health-related quality of life and neurocognition, were not reported.
- Results for the overall survival end points remain to be determined.

Links: [Full Article](#) | [NEJM Quick Take](#) | [Editorial](#) | [Science behind the Study](#)



CONCLUSIONS

Among patients with grade 2 IDH-mutant glioma, progression-free survival was significantly longer with vorasidenib than with placebo.



No. at risk	
Placebo	163 162 161 146 145 145 117 116 114 73 70 65 38 38 29 21 19 9 8 8 4 4 2 2 2 1 0
Vorasidenib	168 166 166 157 154 154 133 131 129 93 91 81 63 63 52 45 45 25 22 20 11 11 11 7 7 4 4 4 0

+ Censored

Alliance A072301:

- **Newly Diagnosed CNS WHO Grade 2 / 3 IDH 1/2 Mutated Glioma**
- **Radiation (54 GY for Grade 2 and 59.4 GY for Grade 3 Tumors)**
- **Followed TMZ + IDH Inhibitor (Ivosidenib) VS TMZ + Placebo**

Alliance A072302:

- **Recurrent IDH 1/2 Mutated Glioma with ATRX Loss**
- **ATR Protein Kinase Inhibitor (ATR Inhibitor): Tuvusertib**
- **Tuvusertib + Pembrolizumab**
- **Tumor Microenvironment - TILS (Tumor Infiltrating Lymphocytes)**

The Future:

- **“This is not the end, not even the beginning of the end, this may be the end of the beginning”**
 - **The Kingsmen**