Pediatric High Grade Glioma

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Pathologic Classification

WHO Classification

- Reference: Louis DN, Perry A, et al., Acta Neuropathol (2016) 131:803-820
- Glioblastoma
  - Glioblastoma, IDH-wildtype
  - Glioblastoma, IDH-mutant
  - Glioblastoma, NOS
- Anaplastic astrocytoma
  - Anaplastic astrocytoma, IDH-wildtype
  - Anaplastic astrocytoma, IDH-mutant
  - Anaplastic astrocytoma, NOS
- Diffuse midline glioma, H3 K27M-mutant
    - Newly defined entity in the 2016 WHO Classification of tumors
    - includes diffuse intrinsic pontine glioma (DIPG)

Pediatric High Grade Glioma

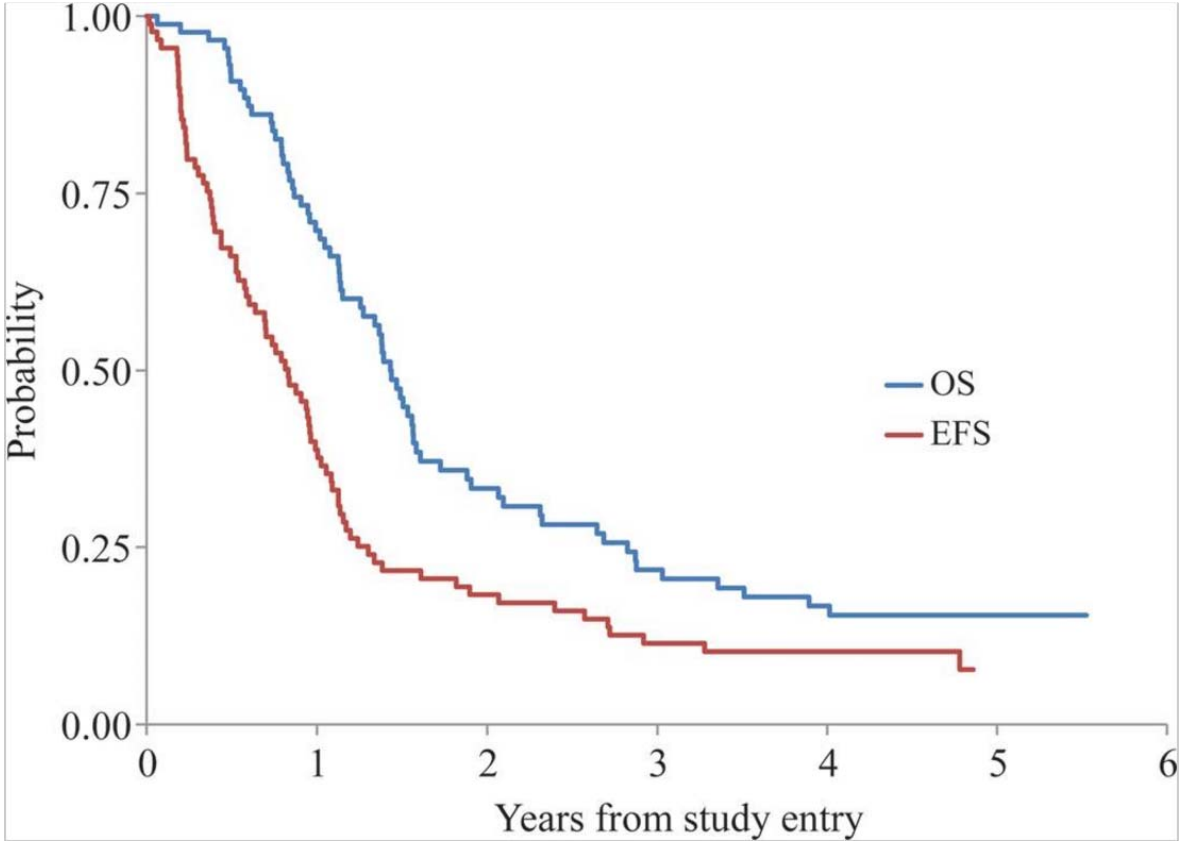
- Pediatric HGGs are genomically distinct from those of adults
- Recent data has demonstrated presence of somatic histone mutations in some pediatric HGGs
  - H3.3 G34R/V mutated tumors found in the cerebral hemispheres
  - H3.3 K27M tumors are distributed along midline (thalamus, brainstem, cerebellum, spine)
  - H3.1 K27M restricted to the pons
    - K27M mutation present in 85% of DIPG patients
    - Now recognized entity in WHO 2016 classification
- However, H3 mutations are found in less than half of pediatric HGGs
  - 5-10% of tumors harbor BRAF V600E mutation
  - <5% harbor IDH1/2 mutations
  - The remaining tumors (nearly 50%) are a heterogenous group with poorly defined markers

Review of Recent Clinical Trials

COG ACNS0126

- Despite improvement in outcome in adult HGG patients with the advent of temozolomide, there has been little change in outcome for pediatric HGG patients in 40 years
- COG ACNS0126 (Cohen KJ, Neuro Oncol, 2011 13(3):317-23)
  - 107 patients, glioblastoma, anaplastic astrocytoma, gliosarcoma
  - Outcomes compared to prior study CCG-945
  - Temozolomide failed to improve outcome
    - 3-year overall survival (OS) 22 ± 5%

COG ACNS0126



COG ACNS0423

- COG ACNS0423 (Jakacki RI, 2016 Neuro Oncol; 18 (10):1442-50.)
  - Concurrent temozolomide and radiation (XRT), CCNU added to TMZ during maintenance, TMZ concurrently with XRT
  - XRT: 54Gy to resection cavity and any residual tumor + 2cm, boost residual tumor + 1cm to total dose 59.4
  - 108 patients, anaplastic astrocytoma and glioblastoma
  - 3-year OS was 28% as compared to 19% in ACNS0126 (p=0.019)

COG ACNS0423

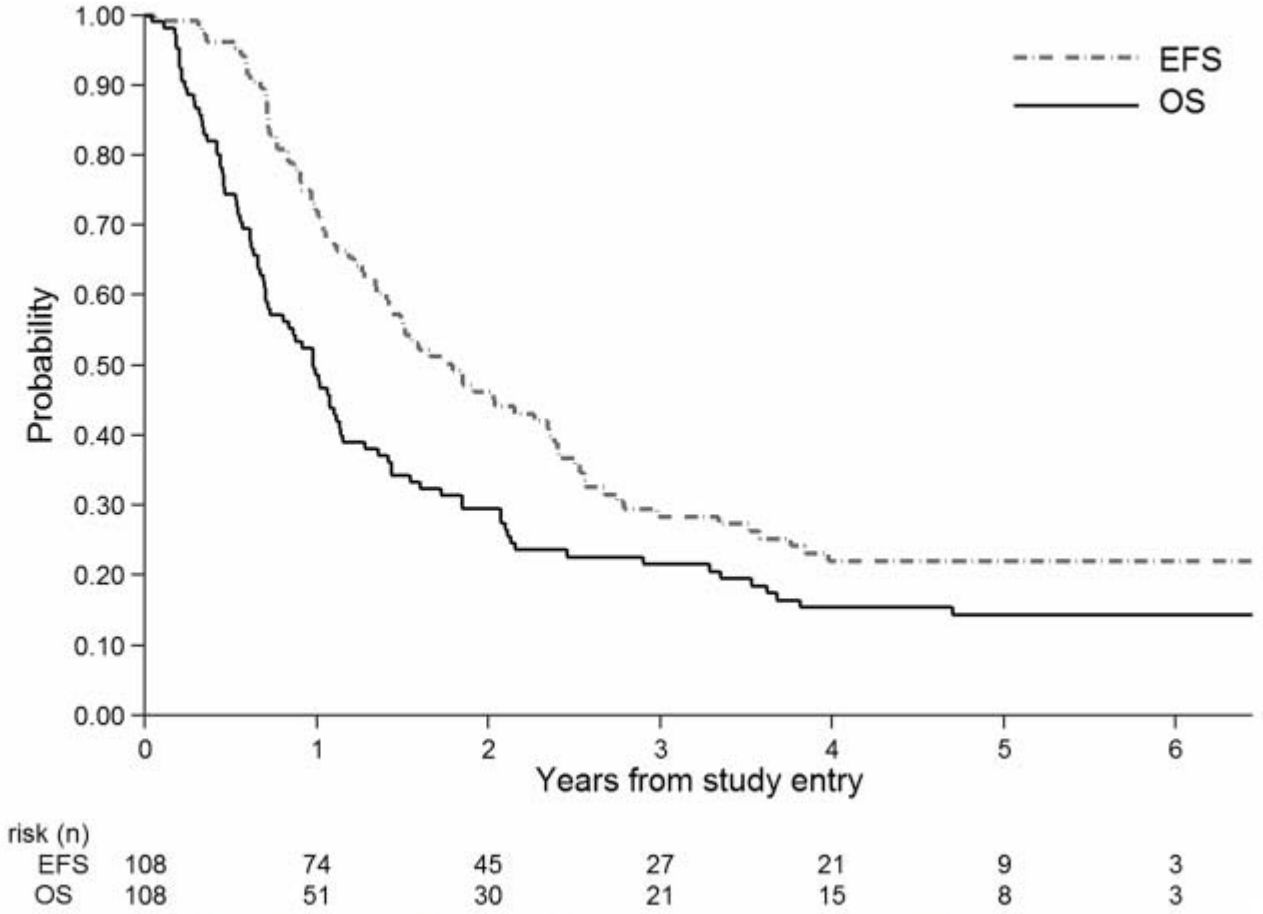


Fig. 1. ACNS0423 EFS (event-free survival) and OS (overall survival) for all participants ($n = 108$).

COG ACNS0822

- COG ACNS0822, most recent COG trial for HGG
  - Control arm: temozolomide + RT
  - Experimental Arms: bevacizumab + RT or vorinostat + RT
  - Design was a “pick-the-winner” to move forward for a phase III trial
  - Study closed in 2014 as no arm showed any superiority

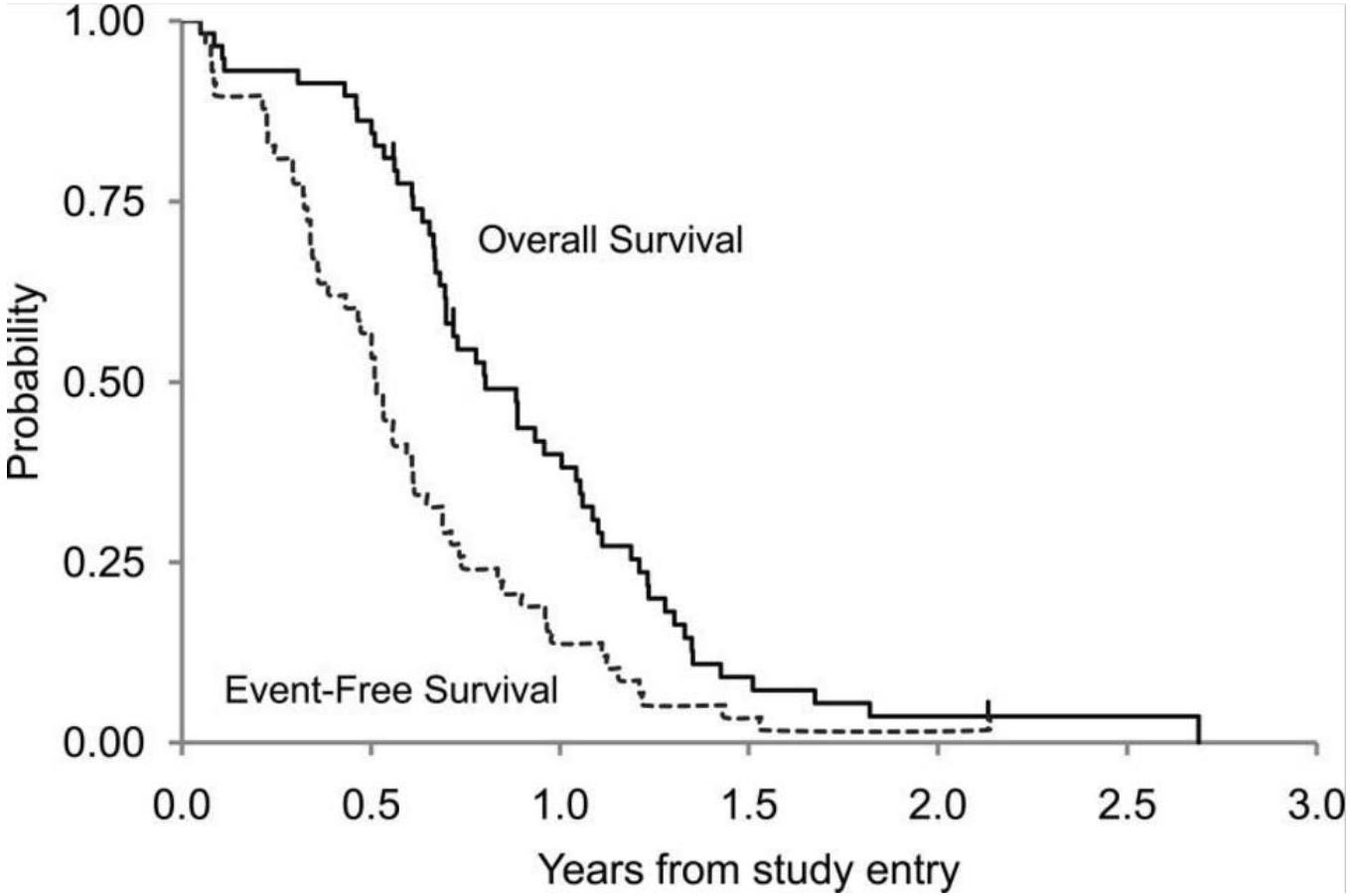
St. Jude HGG Study

- Phase II Trial of Erlotinib (Qaddoumi I, Front Oncol. 2014)
- 41 patients (21 Glioblastoma, 20 Anaplastic astrocytoma)
  - XRT + Erlotinib followed by adjuvant Erlotinib
  - 2 year PFS 15 ± 7% for anplastic astrocytoma and 19 ± 8% for glioblastoma
  - No improvement in outcome compared to historical controls

ANCS0126, DIPG

- 63 DIPG patients (Cohen KJ, Neuro Oncol, 2011;13(4):410-6)
  - Temozolomide + XRT (59.4 Gy) followed by adjuvant temozolomide
  - Median time to death was 9.6 months
  - No improvement over previously reported regimens

ANCS0126, DIPG



COG ACNS0927

- DIPG patients
- Phase 1/2 study of suberoylanilide hydroxamic acid (SAHA, vorinostat) in combination with XRT followed by adjuvant vorinostat
- Vorinostat is an orally bioavailable histone deacetylase (HDAC) inhibitor
- Study is closed to accrual, final results are pending

Selection of currently available clinical trials (2016)

Clinical Trials

- Pacific Pediatric Neuro-Oncology Consortium (PNOC)
  - H3.3K27M Specific Peptide Vaccine Combined with poly-ICLC for the Treatment of newly diagnosed HLA-A2+ H3.3K27M Positive Diffuse Intrinsic Pontine Glioma (DIPG) as well as other newly diagnosed HLA-A2+ H3.3K27M Positive Gliomas
  - A pilot trial testing the feasibility of using molecular profiling to guide an individualized treatment plan in children and young adults with newly diagnosed DIPG
  - Safety and Phase 0 Study of vemurafenib, an oral inhibitor of BRAFV600E, in Children with Recurrent/Refractory BRAFV600E-mutant gliomas

Clinical Trials

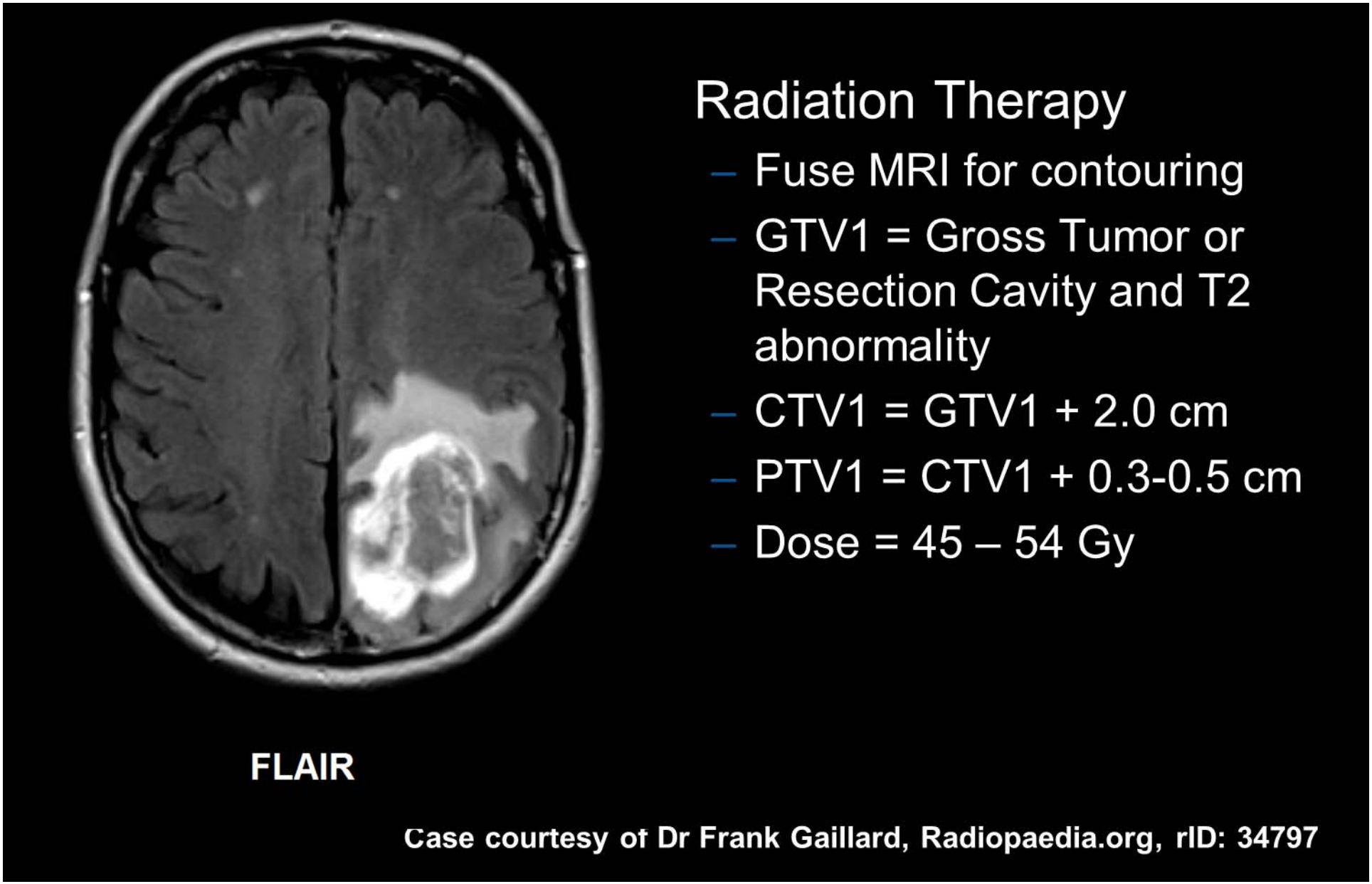
- Children's Oncology Group (COG)
  - A Phase 1 Study of AZD1775 (MK-1775, IND#116459) Concurrent with Local Radiation Therapy for the Treatment of Newly Diagnosed Children with Diffuse Intrinsic Pontine Gliomas
- Pediatric Brain Tumor Consortium (PBTC)
  - A Phase I Trial of Panobinostat in Children with Diffuse Intrinsic Pontine Glioma
  - A Safety and Preliminary Efficacy trial of MK-3475 (pembrolizumab; anti-PD-1) in Children with recurrent, progressive or refractory high-grade gliomas (HGG) and DIPGs

Treatment

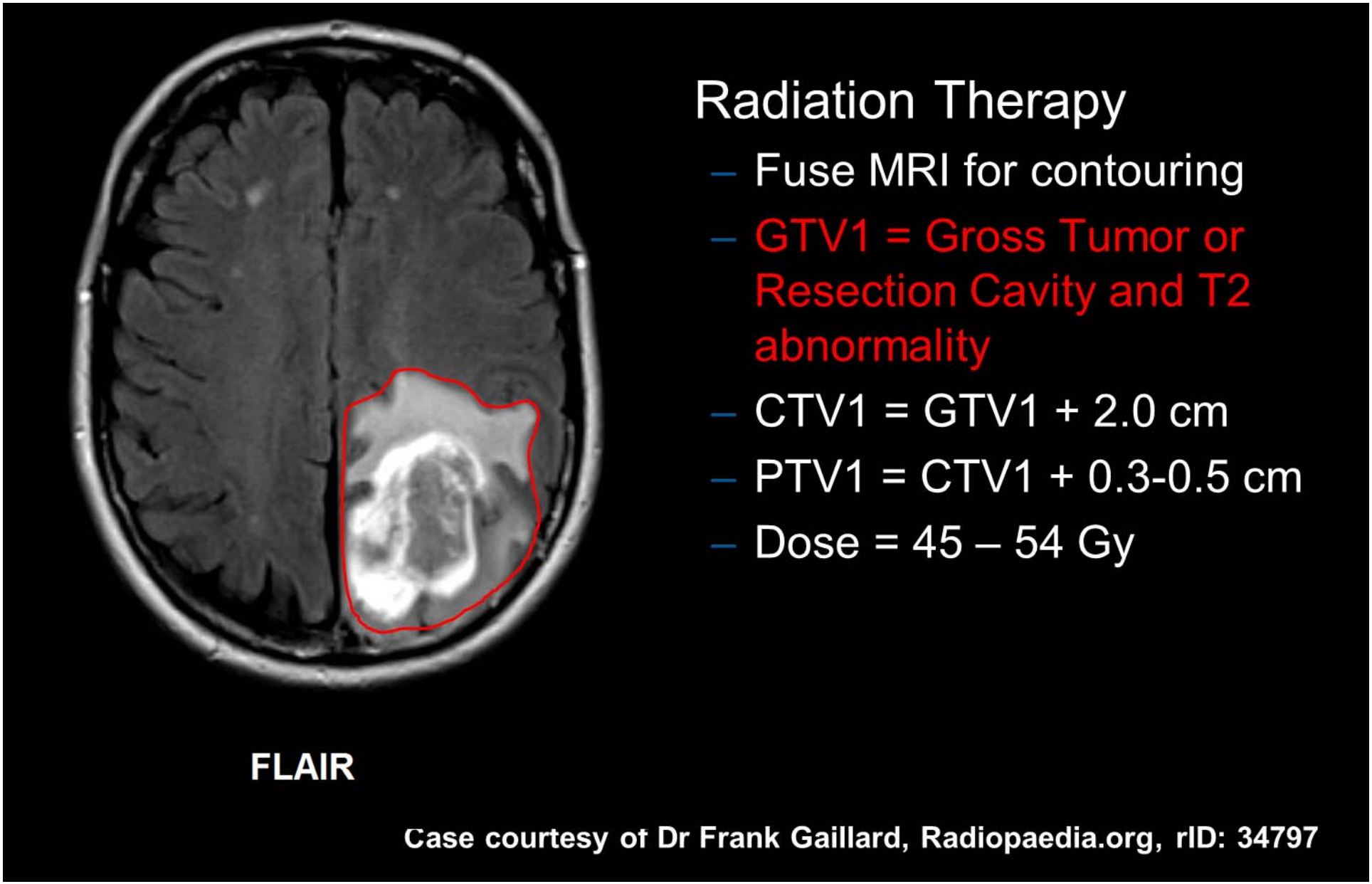
Treatment Glioblastoma/Anaplastic Astrocytoma

- Surgery
  - Maximal safe surgical resection
- Chemotherapy
  - Many institutions consider temozolamide + radiation as standard therapy
- Radiation Therapy

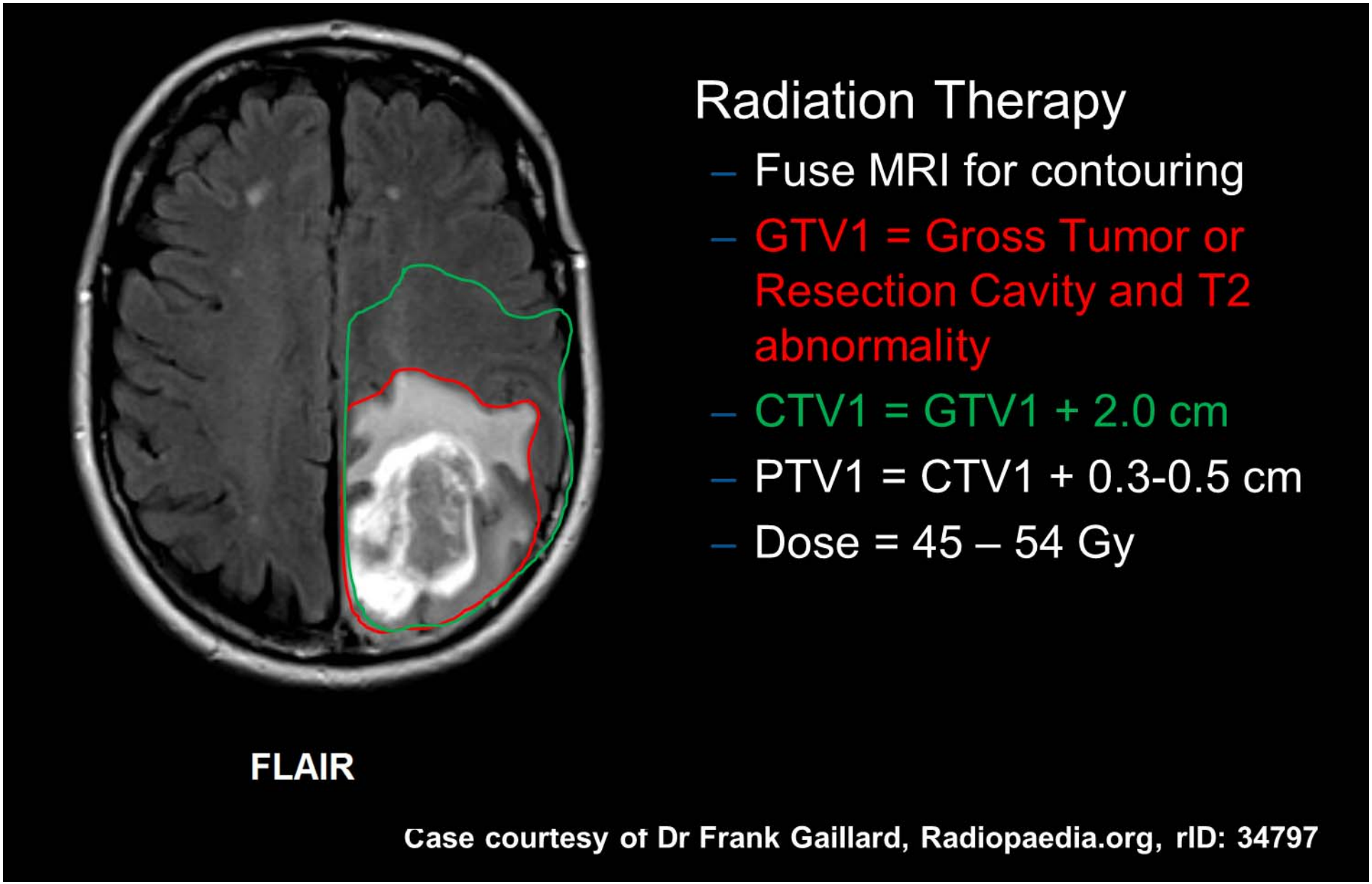
Glioblastoma/Anaplastic Astrocytoma



Glioblastoma/Anaplastic Astrocytoma



Glioblastoma/Anaplastic Astrocytoma



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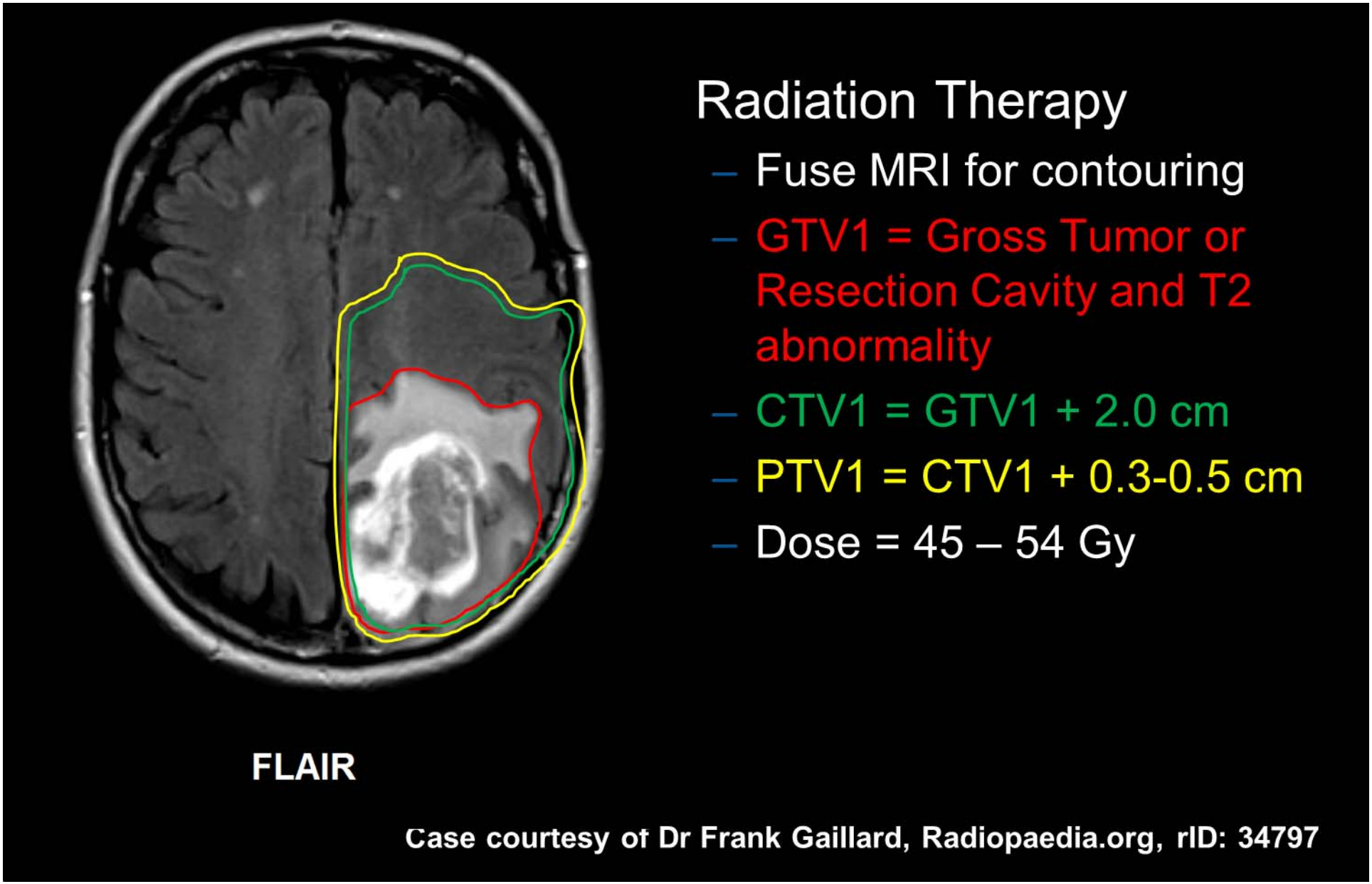

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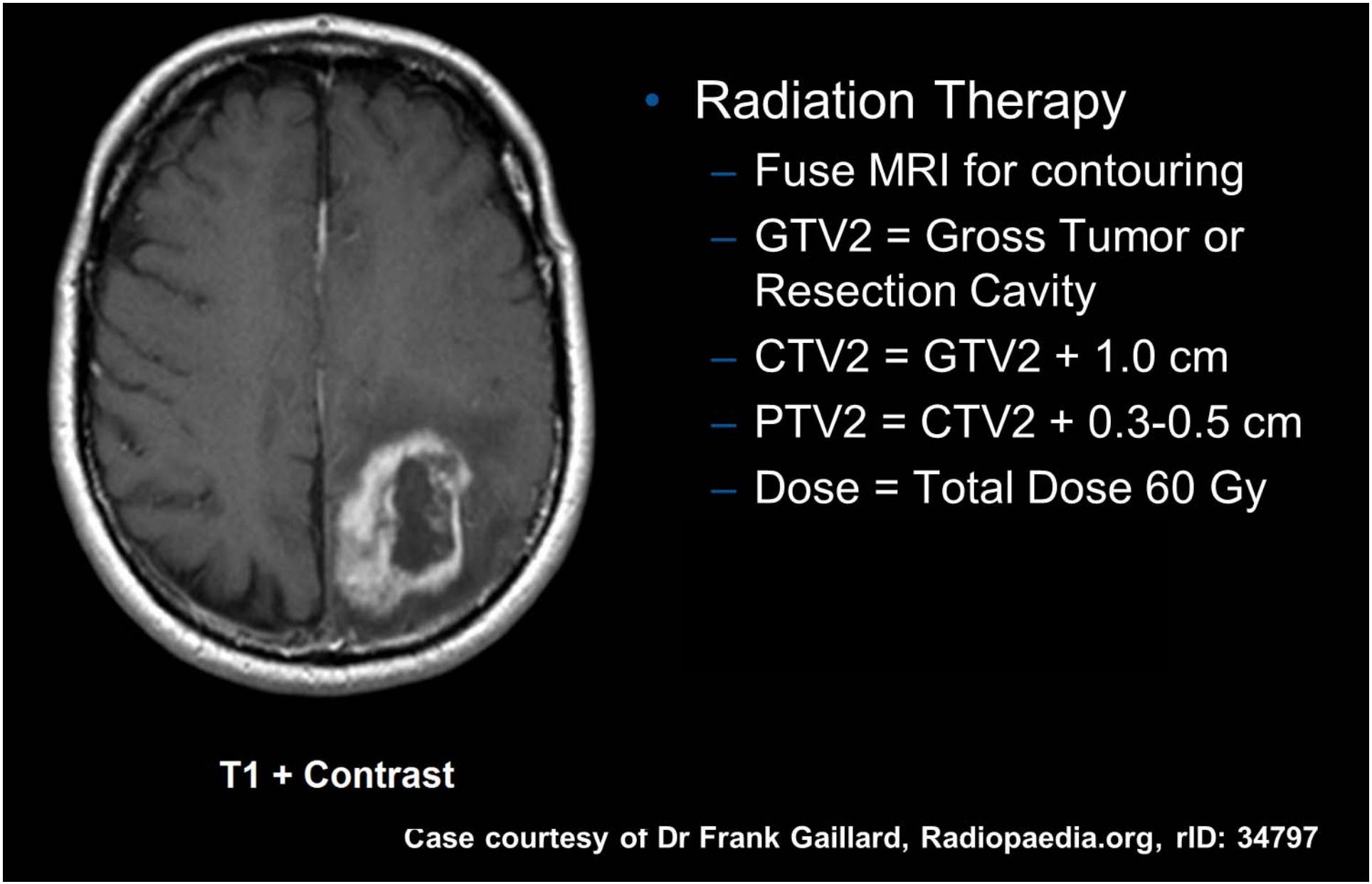

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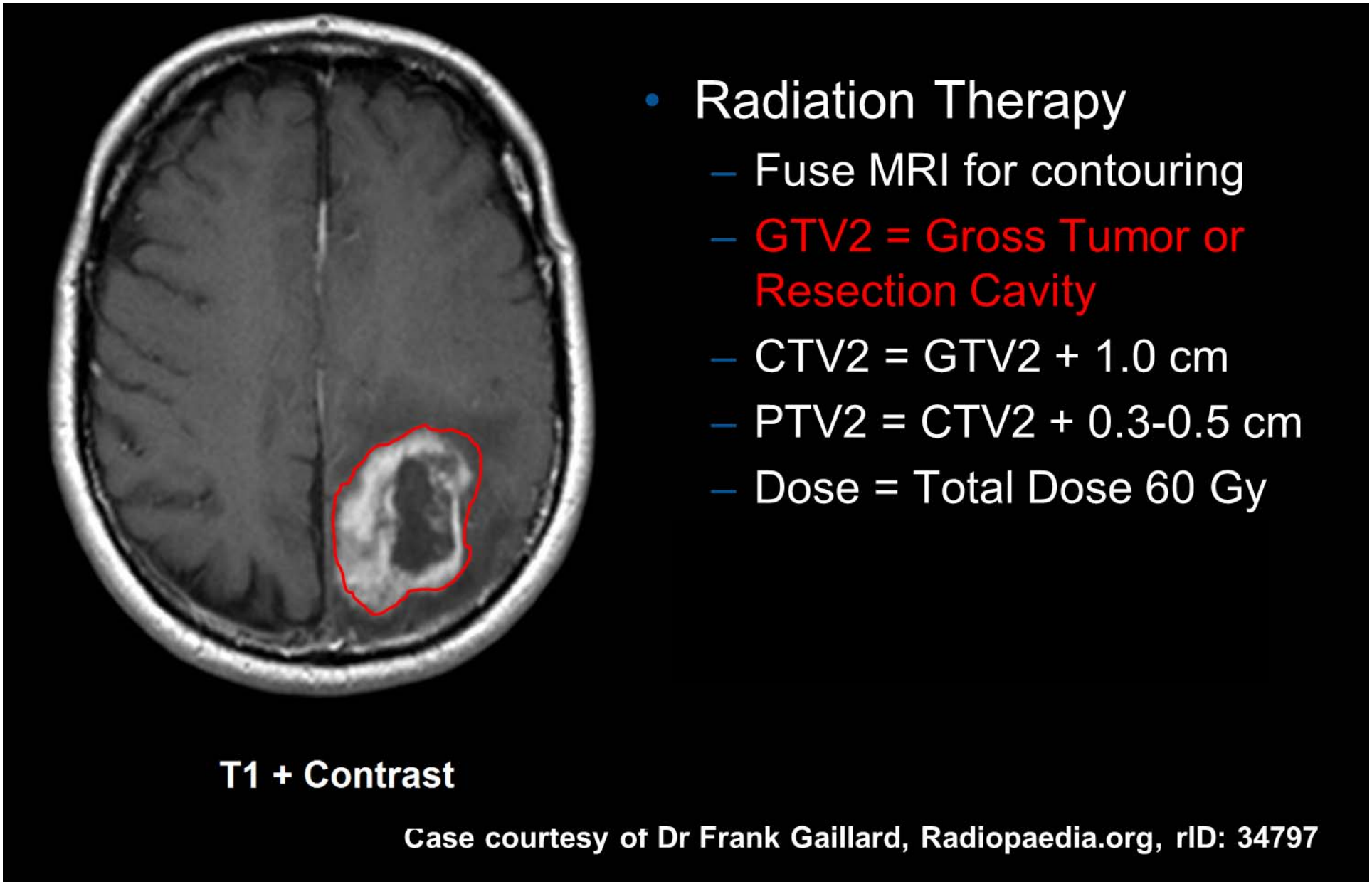
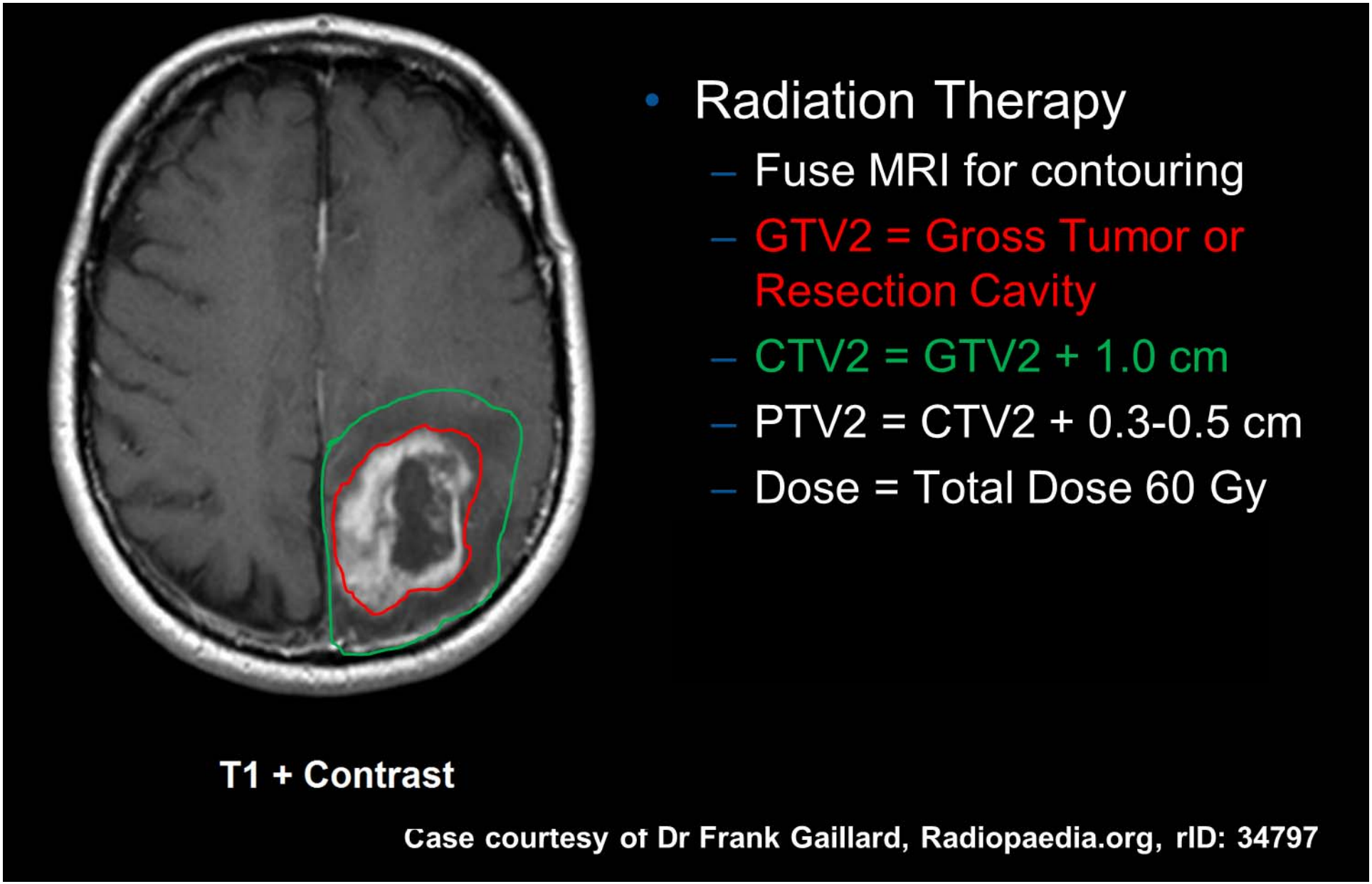
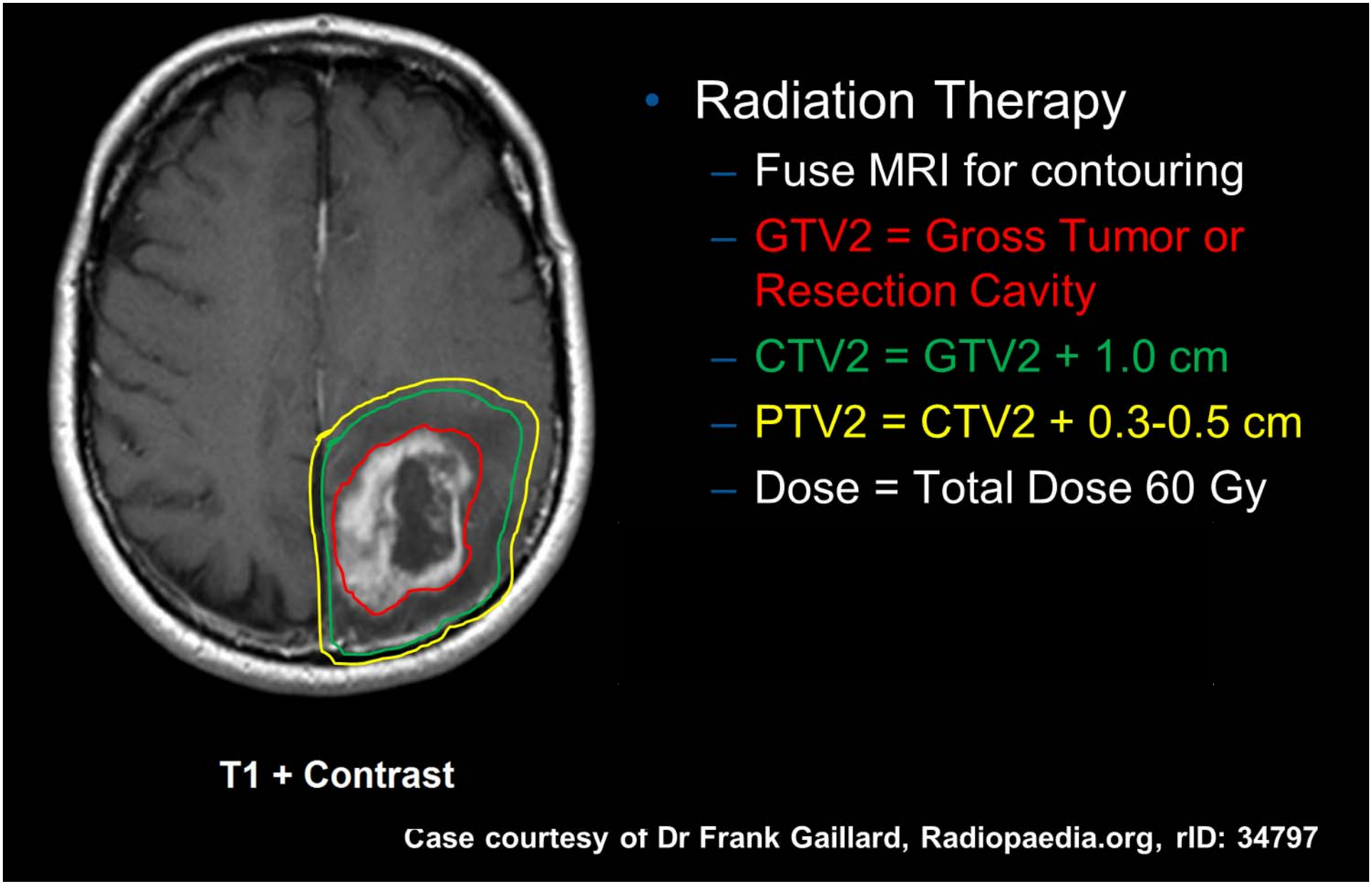


Glioblastoma/Anaplastic Astrocytoma



Glioblastoma/Anaplastic Astrocytoma



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