Radiosurgery for Metastatic Brain Tumors Limits and Outcomes

Robert Wollman, MD

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Brain Metastases

- Outnumber Primary Brain Tumors by more than 10:1
  - Estimate: 100 – 300K / year in US (and rising due to use of MRI and better systemic therapy)
- 20% solitary, 80% multiple @ Dx
- Treatment – symptoms, PS, Histology, # and size mets, systemic disease
  - Surgery, SRS, SRT, WBRT, Drugs, Supportive Care

“Traditional” Therapy: 1990-2000’s

- Surgery for solitary, accessible, and/or symptomatic lesions (Patchell, 1990)
- SRS - 1 – 4 lesions, < 2.5 - 3cm
- SRT - 1 – 4 lesions , > 2.5 - 3 cm
- WBRT > 4 lesions

Whole Brain RT

- Historical mainstay for multiple mets
- Benefit called into question:
  - Poor tolerance in elderly and low PS
  - 3 Randomized trials of Surgery or SRS +/- WBRT showed no survival/QOL advantage despite decrease in brain failure
- Improvement in ability to diagnose and treat numerous small lesions with SRS/SRT (deployment of LINACS/GK, planning systems, frameless rx)

WBRT: QUARTZ Trial

Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial

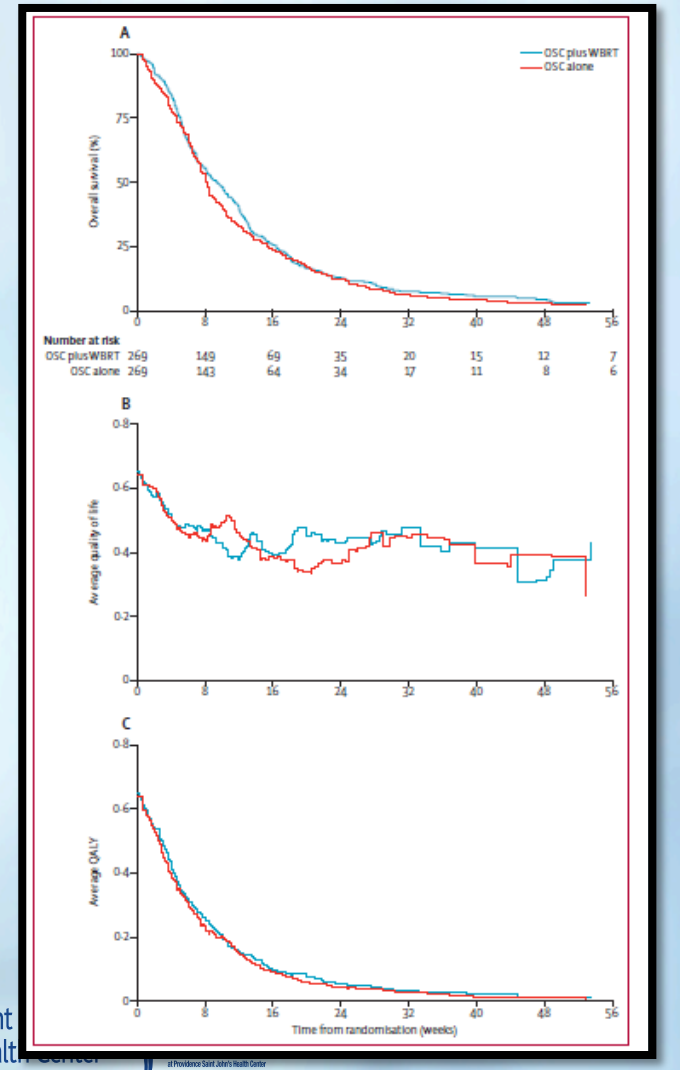
Paula Mulvenna, Matthew Nankivell, Rachael Barton, Corinne Faivre-Finn, Paula Wilson, Elaine McColl, Barbara Moore, Iona Brisbane, David Ardron, Tanya Holt, Sally Morgan, Caroline Lee, Kathryn Waite, Neil Bayman, Cheryl Pugh, Benjamin Sydes, Richard Stephens, Mahesh K Parmar, Ruth E Langley

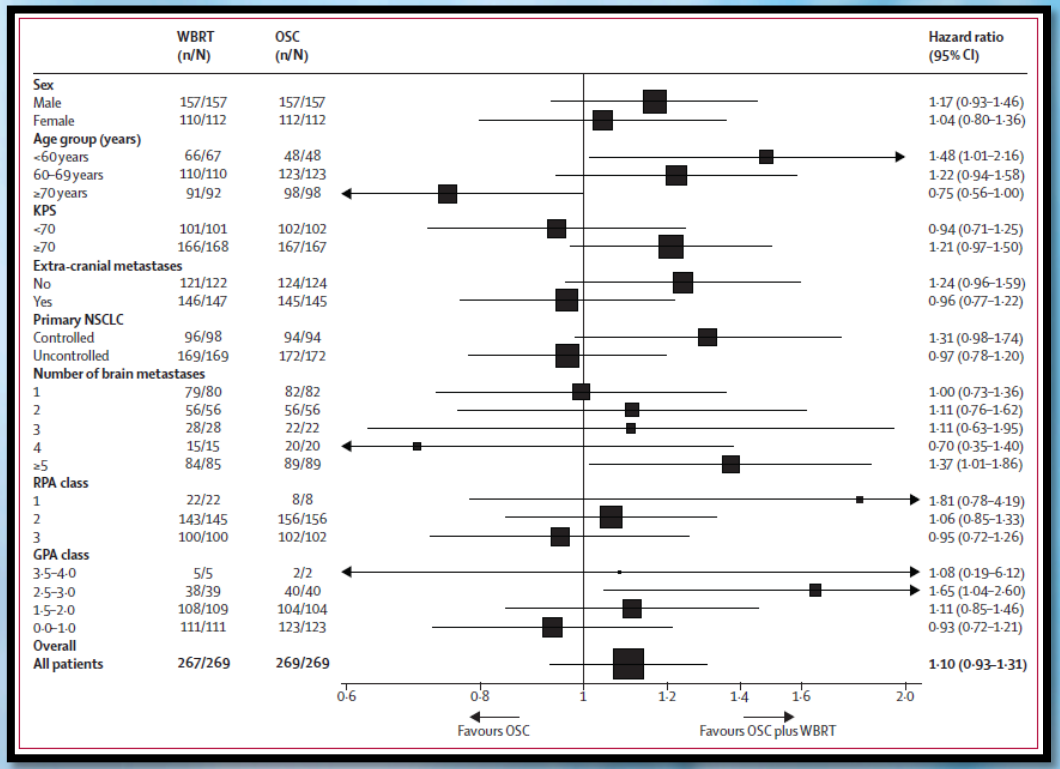
Lancet, 10/2016

WBRT: QUARTZ Trial

- Quality of Life After Treatment for Brain Metastases
  - NSCLC only, UK/Aus. Centers
  - 20 Gy WBRT vs Supportive care
  - Overall – no improvement in survival, steroid use, QALY but OS was very poor (50% 8 weeks)
  - Subgroup – patients younger than 60, good PS, and controlled systemic disease MAY have survival and QALY benefit

WBRT: QUARTZ Trial





"Improved survival with WBRT was shown for younger patients, particularly those Aged younger than 60 years (figure 3, appendix p 6). Other, non-significant, associations also suggested a potential survival benefit with WBRT for patients with good performance status and a controlled primary NSCLC"

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JLGK0901: SRS for > 4 mets

- Japanese GammaKnife Consortium (23 centers, ‘09-’12)
- 1194 patients with 1- 10 mets treated with SRS (no-WBRT upfront)
- Prospective Observational Noninferiority Study to examine OS 1 vs. 2-4 vs. 5-10 lesions

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Lancet, 4/2014

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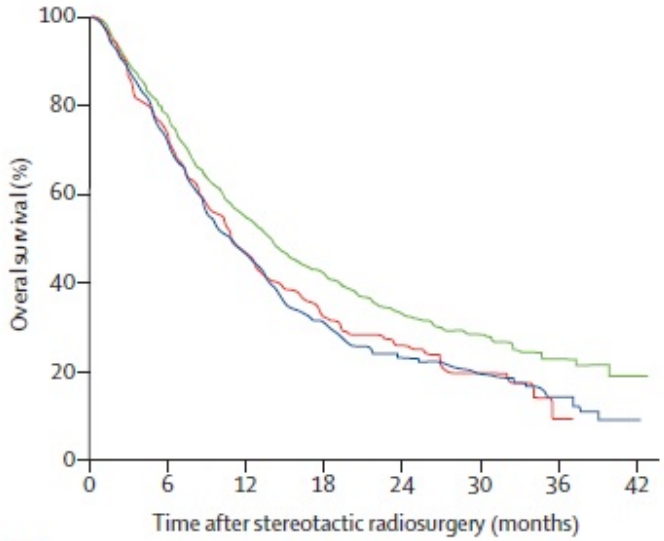
JLGK0901: SRS for > 4 mets

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78



Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

Figure: **Kaplan-Meier curves of overall survival**
HR=hazard ratio.

- OS 13.9 m (1 met) and 10.8 m (2-4 AND 5-10 mets)
- No measure diff. in Secondary Endpoints for 2-4 and 5-10 (neuro death, LR, new lesions, LMD, salvage SRS or WBRT, neurocognitive fxn)

Lancet, 4/2014

www.jkns.or.kr 10.3340/jkns.2008.44.6.358
Print ISSN 2005-3711 On-line ISSN 1598-7876
J Korean Neurosurg Soc 44 : 358-363, 2008

Clinical Article

Gamma Knife Radiosurgery for Ten or More Brain Metastases

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Objective : This study was performed to assess the efficacy of GKS in patients with ten or more brain metastases.

Methods : From Aug 2002 to Dec 2007, twenty-six patients (13 men and 13 women) with ten or more cerebral metastatic lesions underwent GKS. The mean age was 55 years (32-80). All patients had Karnofsky performance status (KPS) score of 70 or better. According to recursive partitioning analysis (RPA) classification, 3 patients belonged to class I and 23 to class II. The location of primary tumor was lung (21), breast (3) and unknown (2). The mean number of the lesions per patient was 16.6 (10-37). The mean cumulated volume was 10.9 cc (1.0-42.2). The median marginal dose was 15 Gy (9-23). Overall survival and the prognostic factors for the survival were retrospectively analyzed by using Kaplan Meier method and univariate analysis.

Results : Overall median survival from GKS was 34 weeks (8-199). Local control was possible for 79.5% of the lesions and control of all the lesions was possible in at least 14 patients (53.8%) until 6 months after GKS. New lesions appeared in 7 (26.9%) patients during the same period. At the last follow-up, 18 patients died; 6 (33.3%) from systemic causes, 10 (55.6%) from neurological causes, and 2 (11.1%) from unknown causes. Synchronous onset in non-small cell lung cancer (p=0.007), high KPS score ($\geq$80, p=0.029), and controlled primary disease (p=0.020) were favorable prognostic factors in univariate analysis.

Conclusion : In carefully selected patients, GKS may be a treatment option for ten or more brain metastases.

KEY WORDS : Multiple · Brain metastases · Gamma knife radiosurgery · Prognostic factor.

Stereotactic radiosurgery using the Leksell Gamma Knife Perfexion unit in the management of patients with 10 or more brain metastases

Clinical article

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Departments of [1]Neurological Surgery and [2]Radiation Oncology; [3]Center for Image-Guided Neurosurgery; and [4]University of Pittsburgh Cancer Institute , University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Object. To better establish the role of stereotactic radiosurgery (SRS) in treating patients with 10 or more intracranial metastases, the authors assessed clinical outcomes and identified prognostic factors associated with survival and tumor control in patients who underwent radiosurgery using the Leksell Gamma Knife Perfexion (LGK PFX) unit.

Methods. The authors retrospectively reviewed data in all patients who had undergone LGK PFX surgery to treat 10 or more brain metastases in a single session at the University of Pittsburgh. Posttreatment imaging studies were used to assess tumor response, and patient records were reviewed for clinical follow-up data. All data were collected by a neurosurgeon who had not participated in patient care.

Results. Sixty-one patients with 10 or more brain metastases underwent SRS for the treatment of 806 tumors (mean 13.2 lesions). Seven patients (11.5%) had no previous therapy. Stereotactic radiosurgery was the sole prior treatment modality in 8 patients (13.1%), 22 (36.1%) underwent whole-brain radiation therapy (WBRT) only, and 16 (26.2%) had prior SRS and WBRT. The total treated tumor volume ranged from 0.14 to 40.21 cm^3, and the median radiation dose to the tumor margin was 16 Gy. The median survival following SRS for 10 or more brain metastases was 4 months, with improved survival in patients with fewer than 14 brain metastases, a nonmelanomatous primary tumor, controlled systemic disease, a better Karnofsky Performance Scale score, and a lower recursive partitioning analysis (RPA) class. Prior cerebral treatment did not influence survival. The median survival for a patient with fewer than 14 brain metastases, a nonmelanomatous primary tumor, and controlled systemic disease was 21.0 months. Sustained local tumor control was achieved in 81% of patients. Prior WBRT predicted the development of new adverse radiation effects.

Conclusions. Stereotactic radiosurgery safely and effectively treats intracranial disease with a high rate of local control in patients with 10 or more brain metastases. In patients with fewer metastases, a nonmelanomatous primary lesion, controlled systemic disease, and a low RPA class, SRS may be most valuable. In selected patients, it can be considered as first-line treatment.

(http://thejns.org/doi/abs/10.3171/2012.4.JNS11870)

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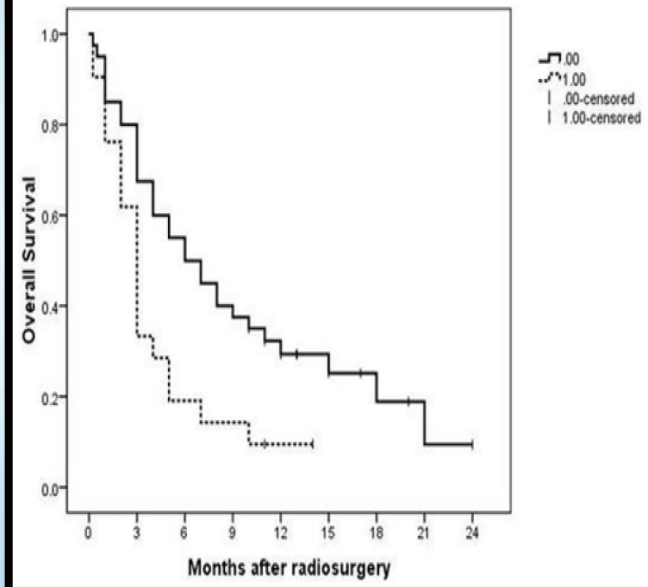

FIG. 2. Kaplan-Meier plot showing overall survival after radiosurgery according to the number of brain metastases. Patients with fewer than 14 brain metastases had significantly longer survivals after radiosurgery ($p = 0.03$).

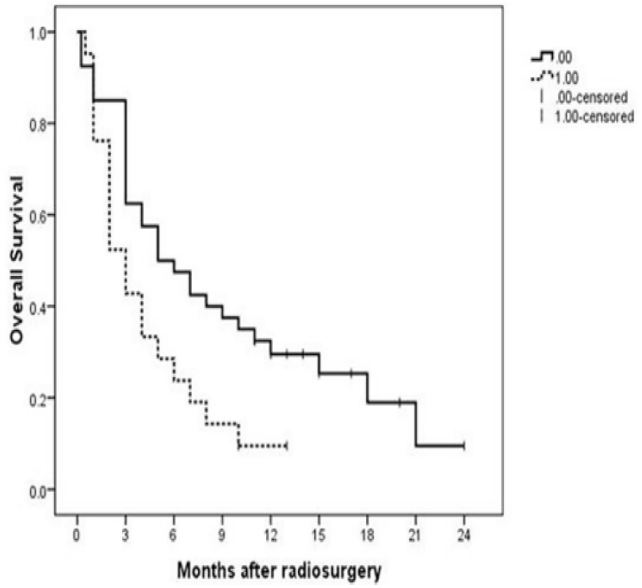

FIG. 3. Kaplan-Meier plot showing overall survival after radiosurgery according to tumor type. Patients with a primary tumor type other than melanoma had significantly longer survival after radiosurgery ($p = 0.009$).

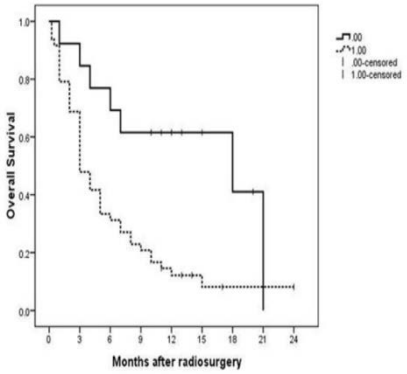

FIG. 4. Kaplan-Meier plot showing overall survival after radiosurgery according to extracranial disease status. Patients with controlled extracranial disease had significantly longer survival after radiosurgery ($p = 0.04$).

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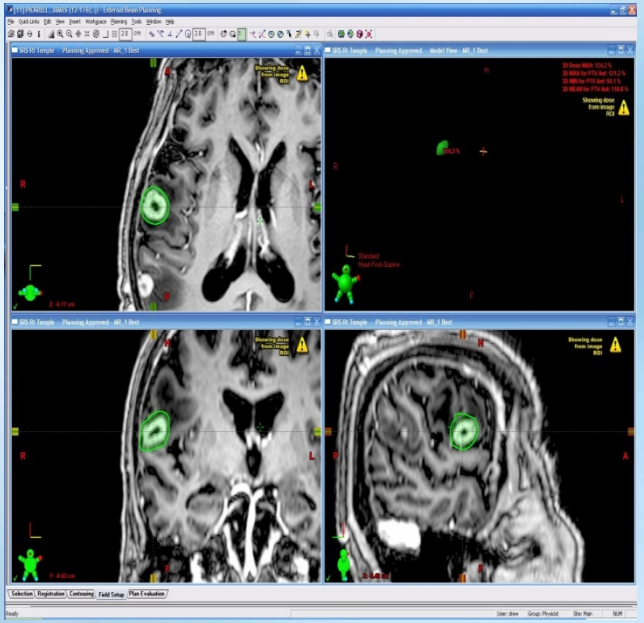

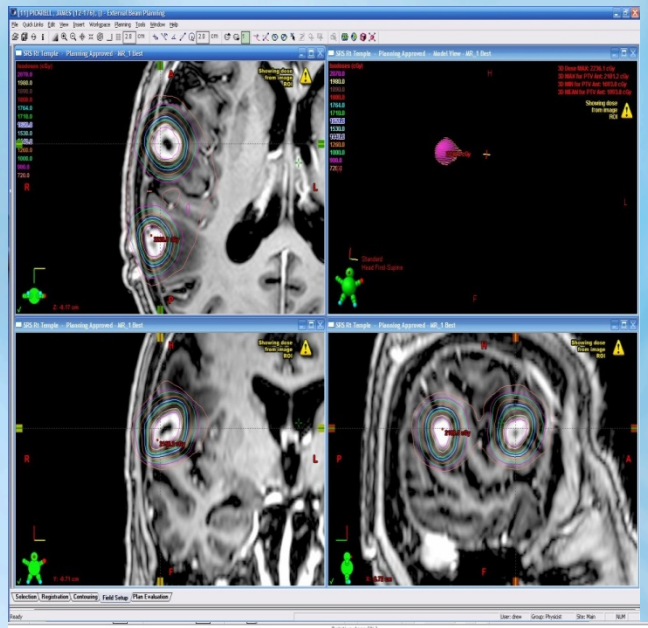

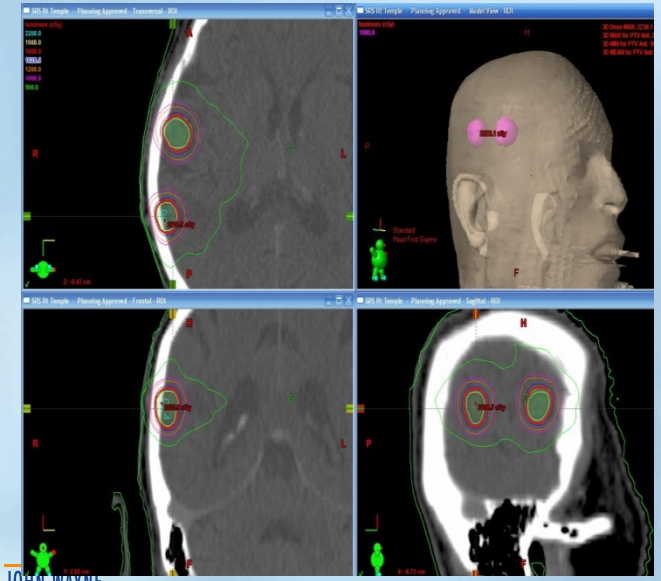

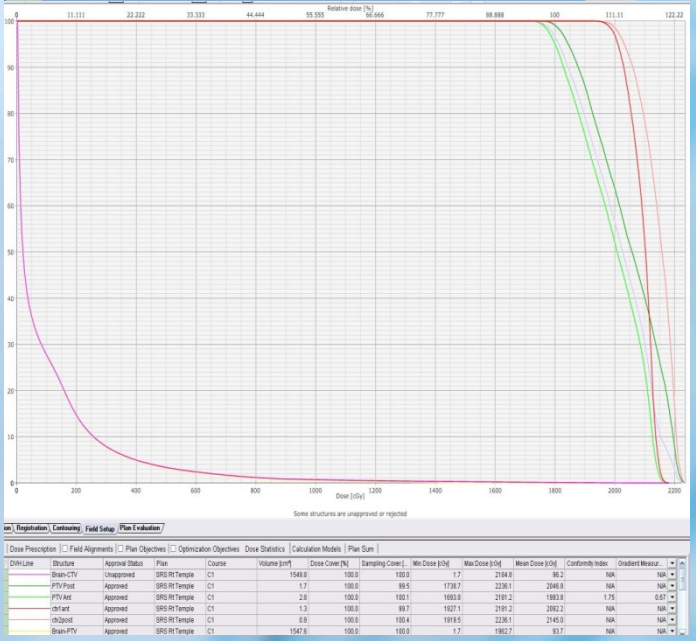

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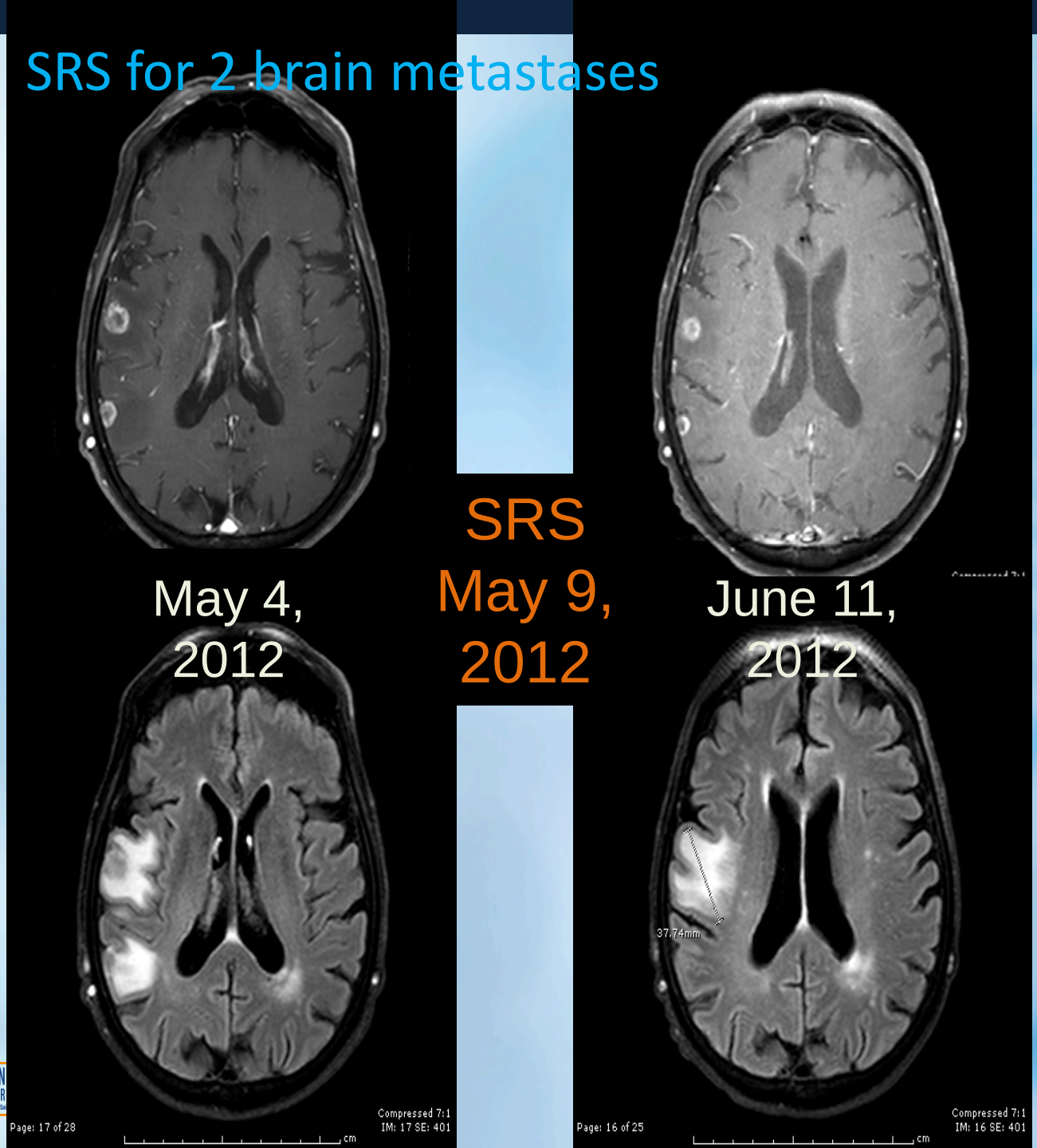
SRS for 2 brain metastases



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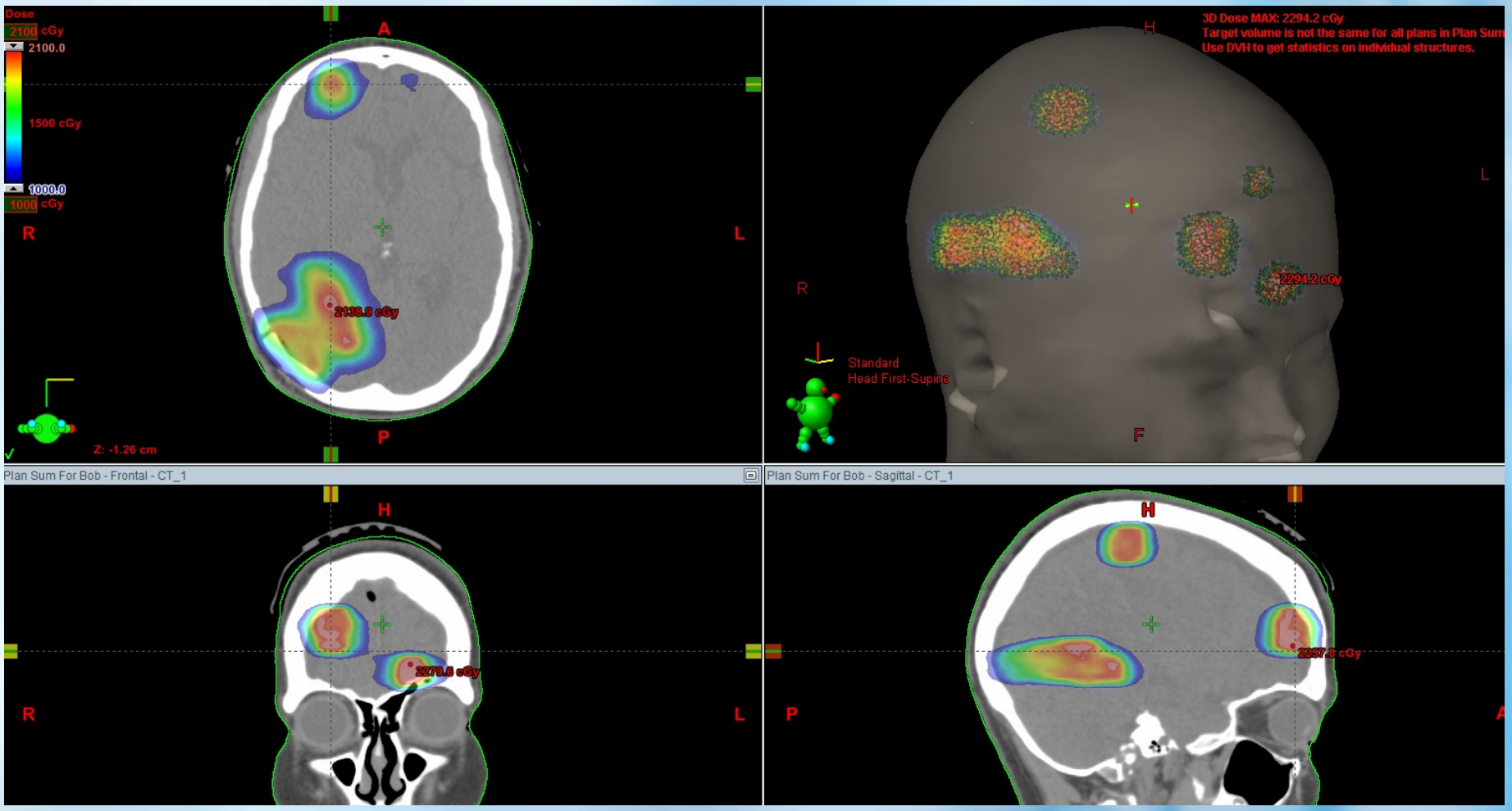

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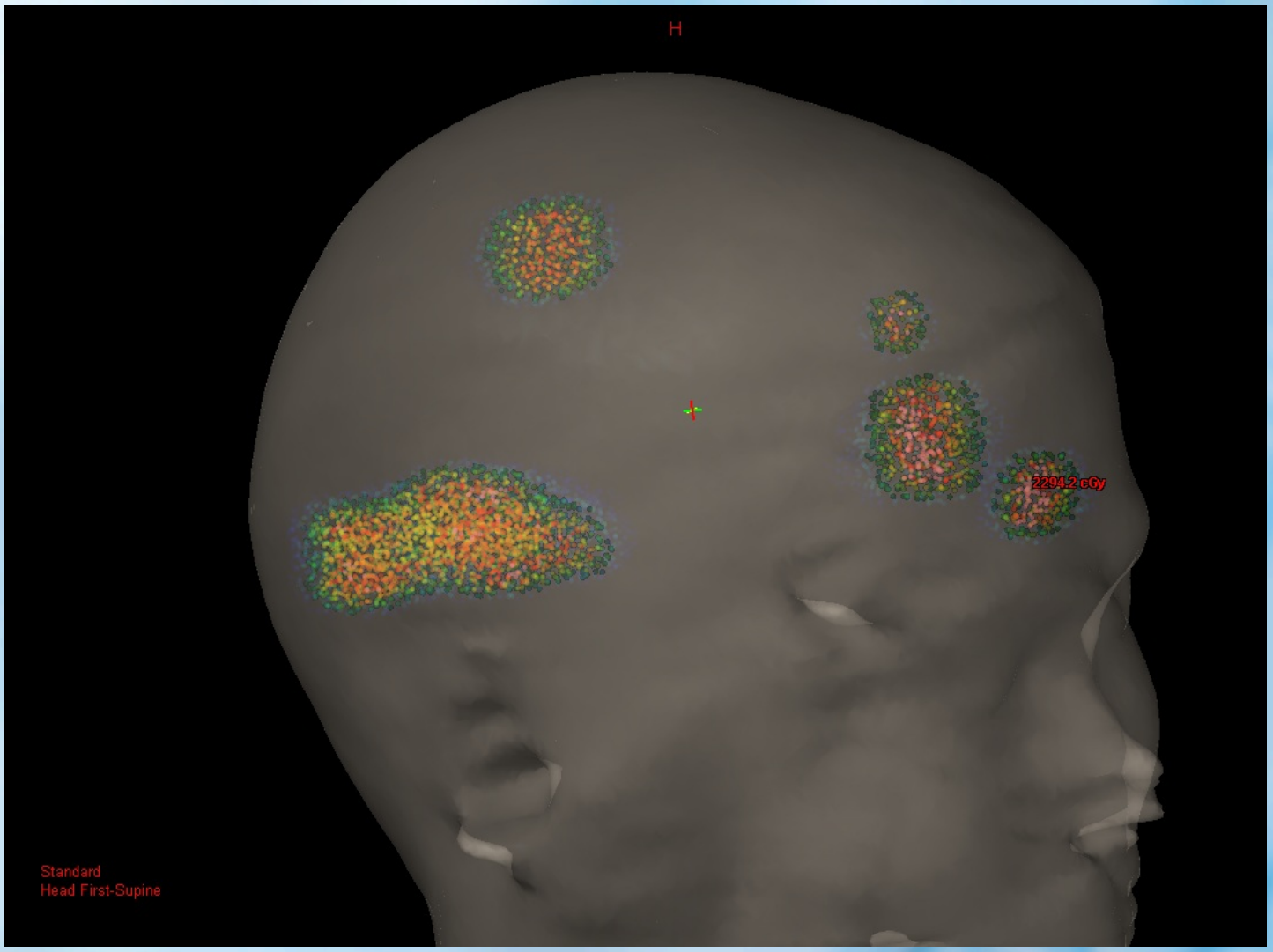

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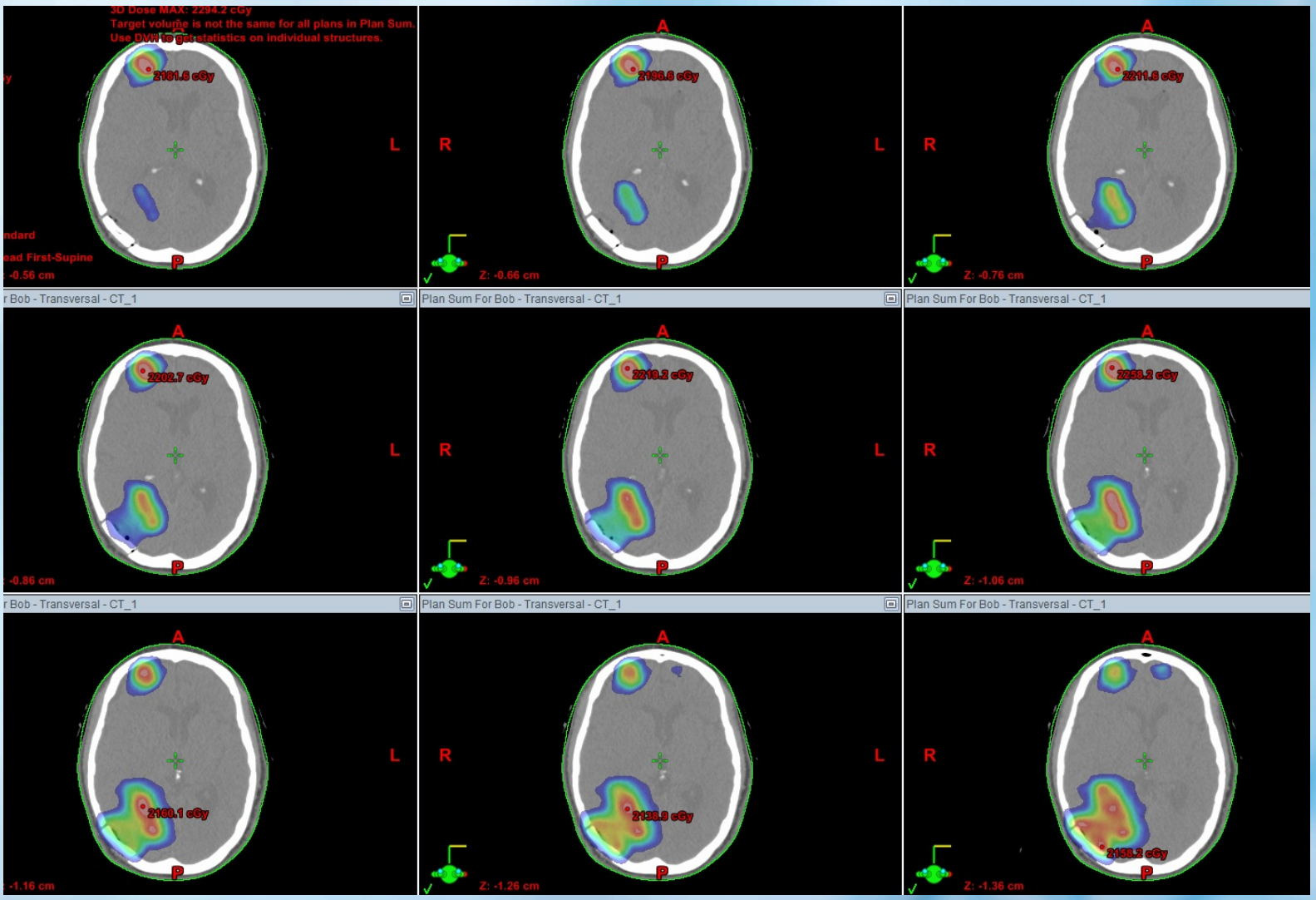

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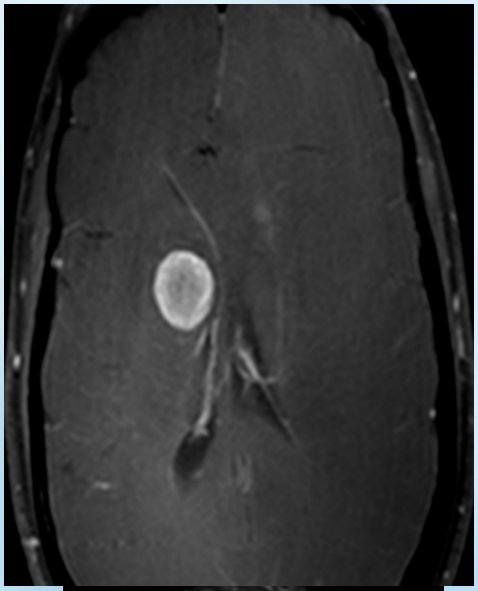
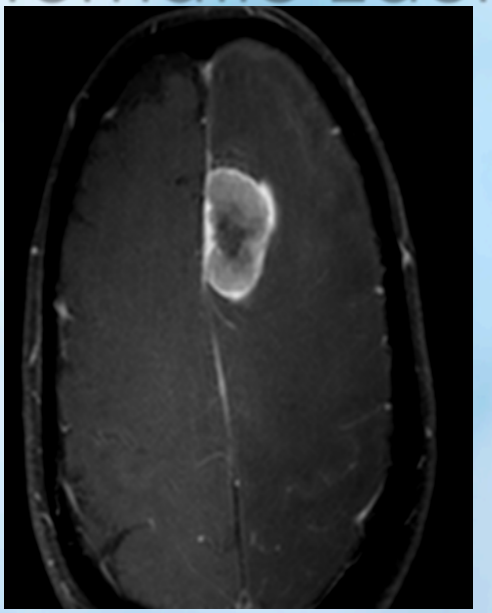
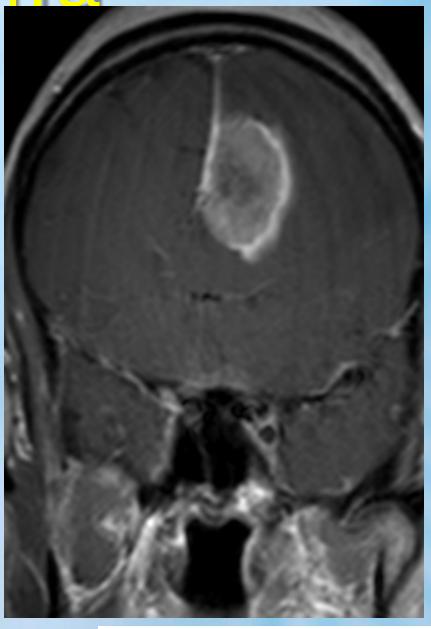
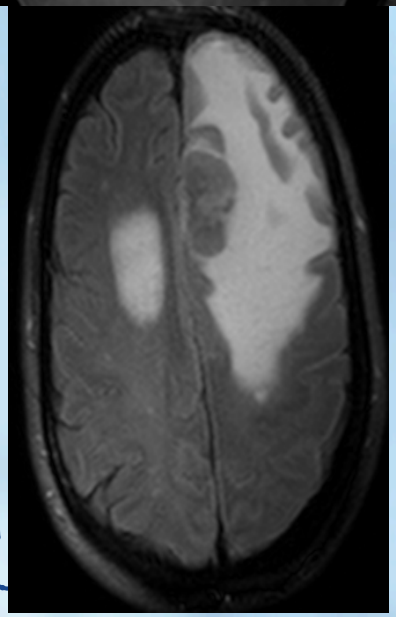
Metastatic Bladder Carcinoma:
2 Mets with Symptomatic Edema

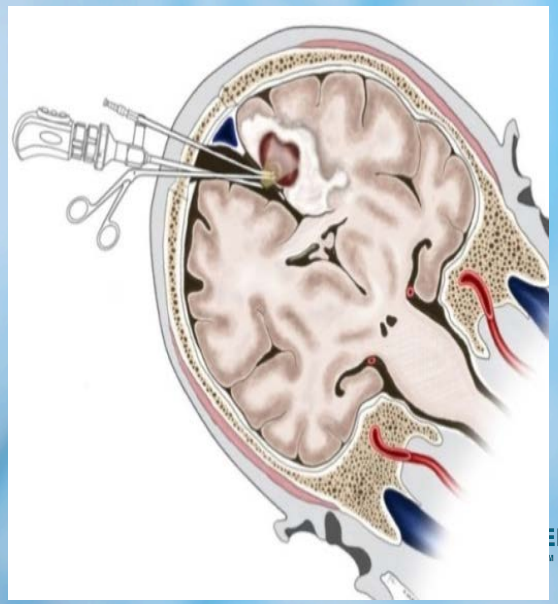








Surgical resection of larger symptomatic met and SRS to both lesions



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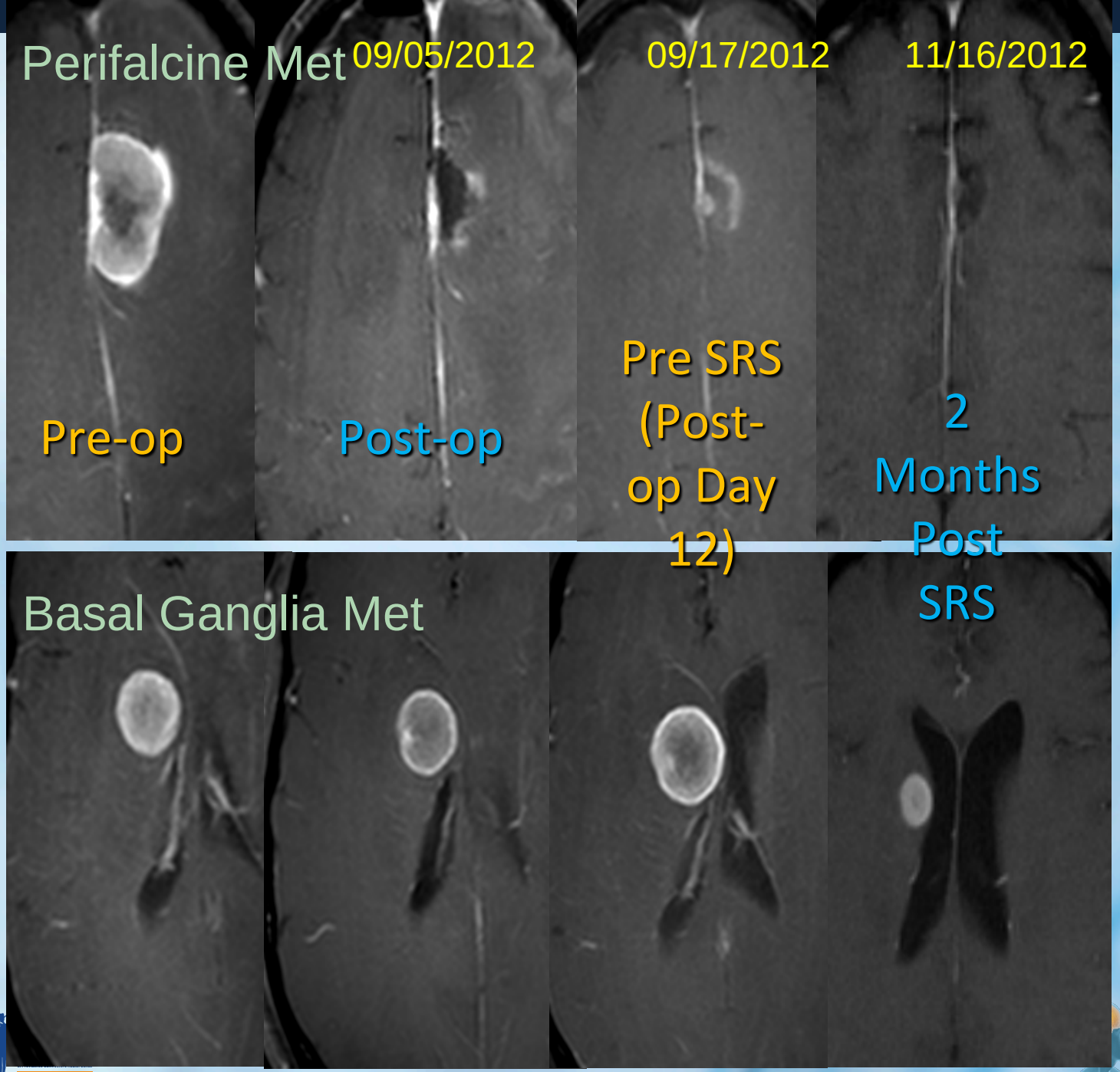
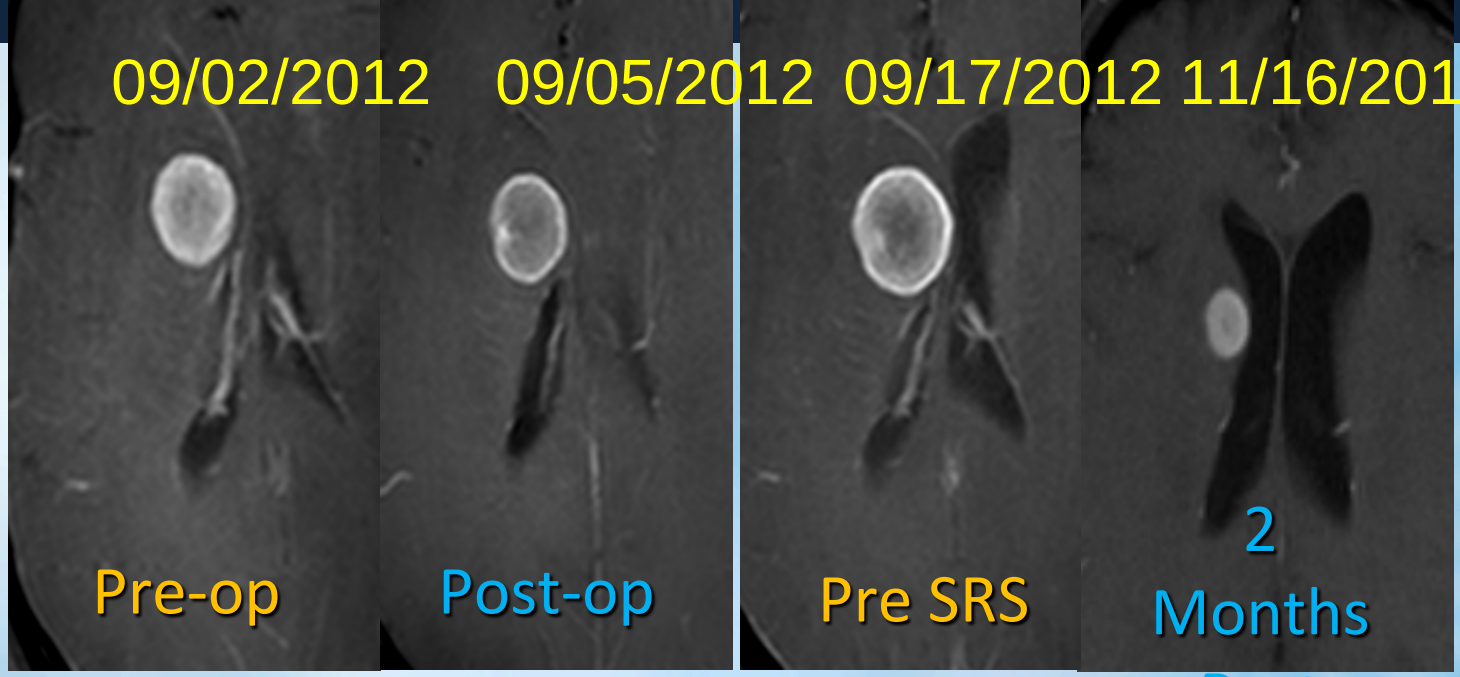
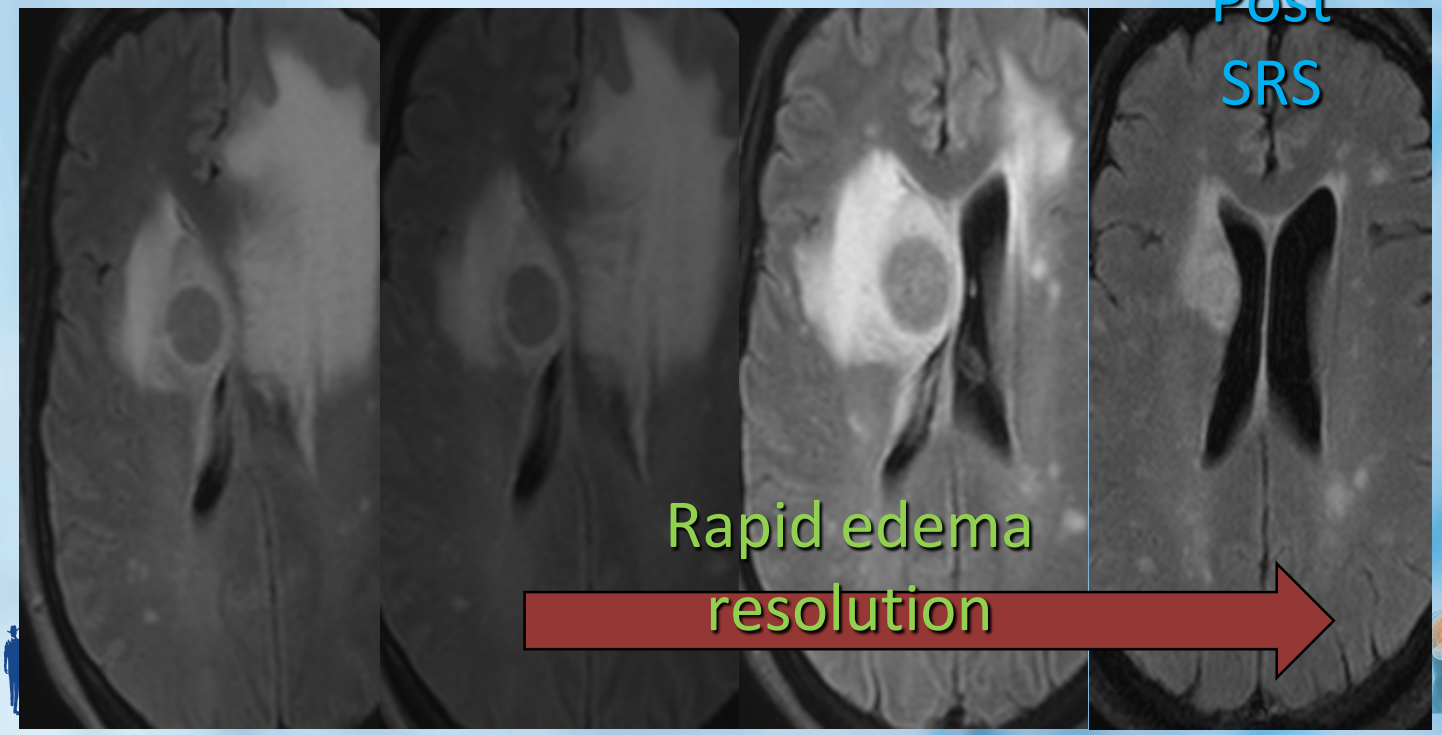

Perifalcine Met
09/05/2012
09/17/2012
11/16/2012
Pre-op
Post-op
Pre SRS (Post-op Day 12)
2 Months Post SRS
Basal Ganglia Met





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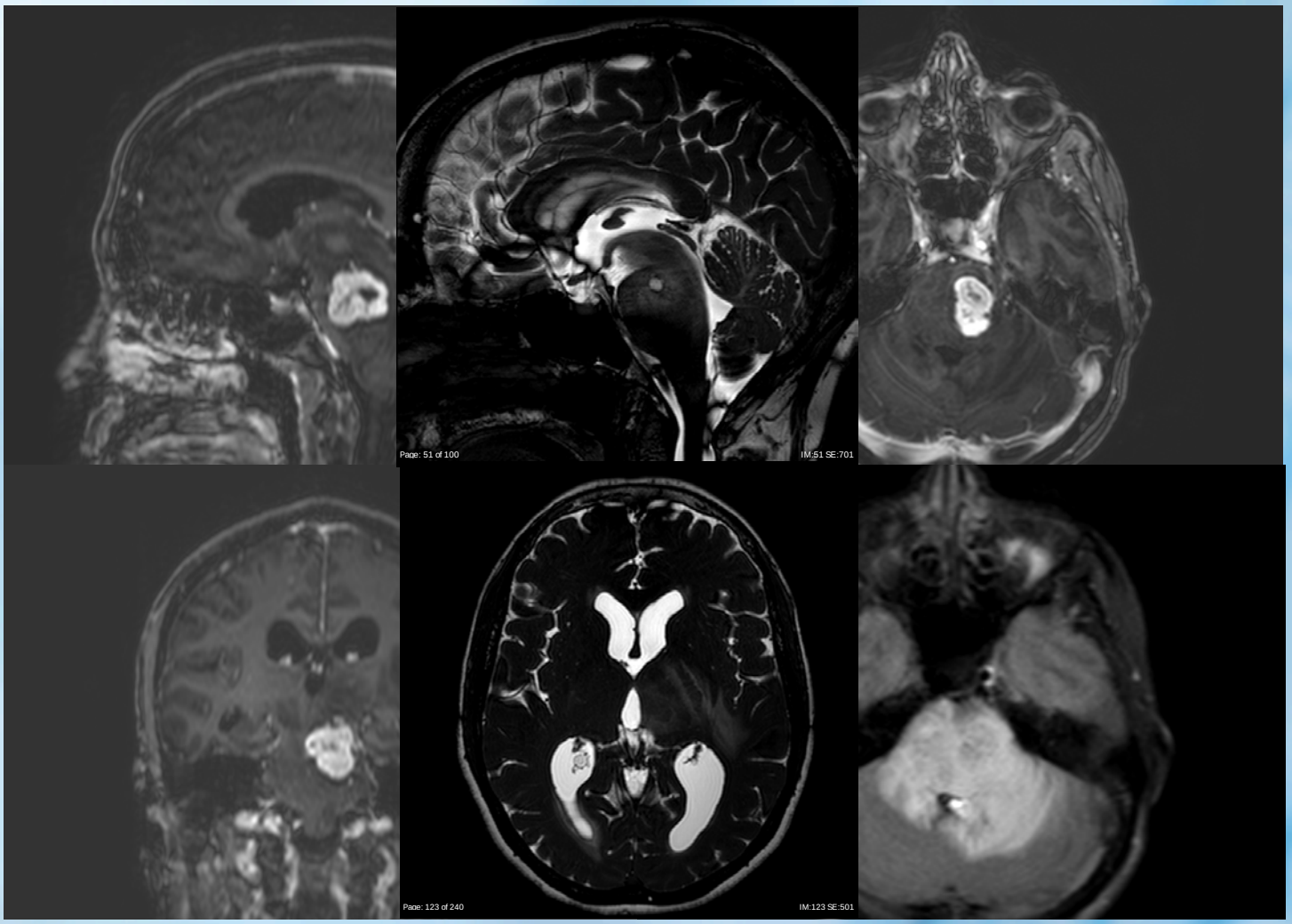
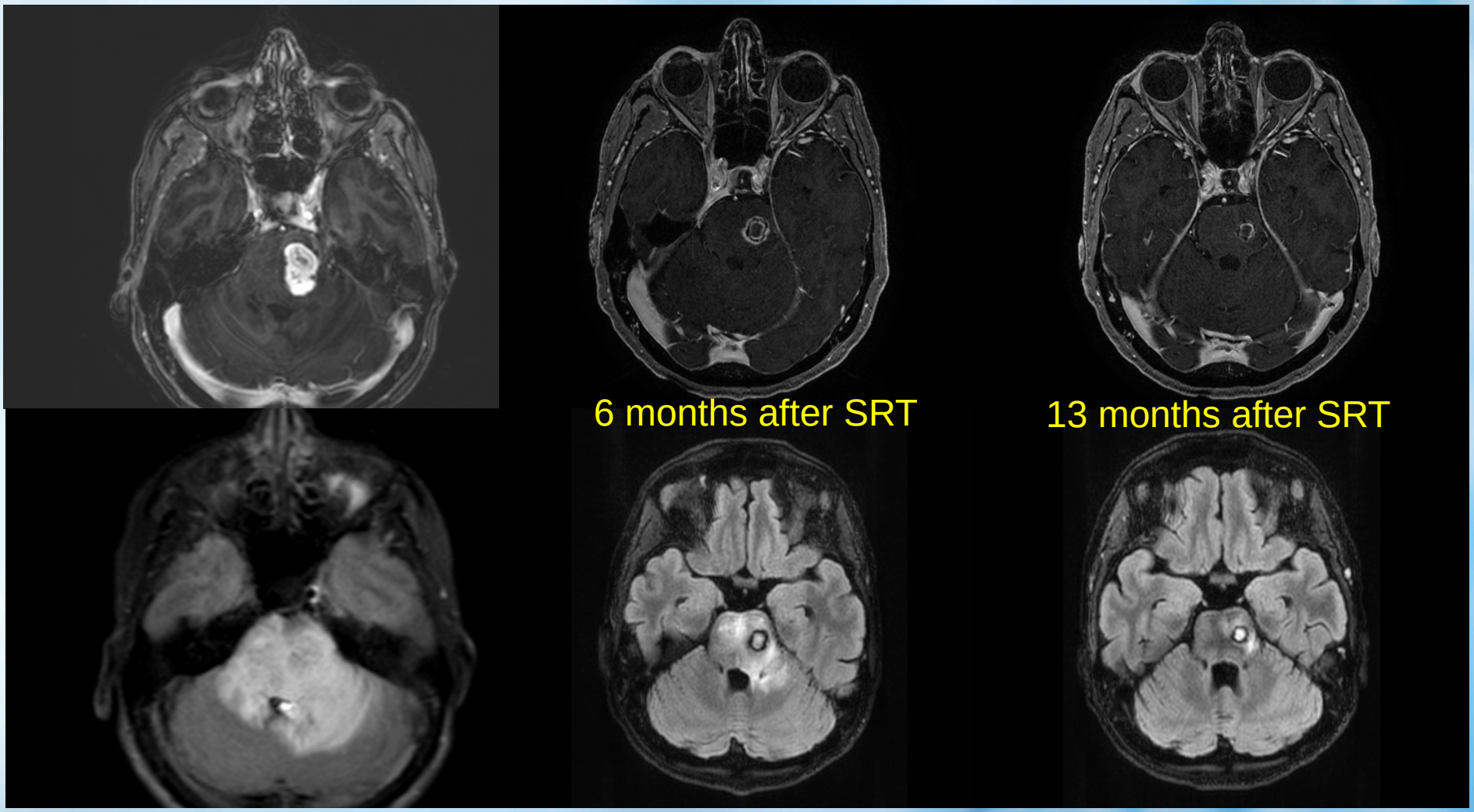
60F with metastatic Renal Cell Carcinoma with multiple falls, Pontine brainstem mass and hydrocephalus



Hydrocephalus treated with endoscopic third ventriculostomy (ETV). Tumor treated with 5400cGy/30Fx



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