

# EACH BRAIN METASTASIS DECISION THROUGH THE DISEASE COURSE, STEP BY STEP....

Or wherever you go, there you are.....

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# Conflicts of interest

- Research Support: Incyte, Novartis, Novocure, BMS
- Steering Committees/Advisory Boards: Novocure and Servier

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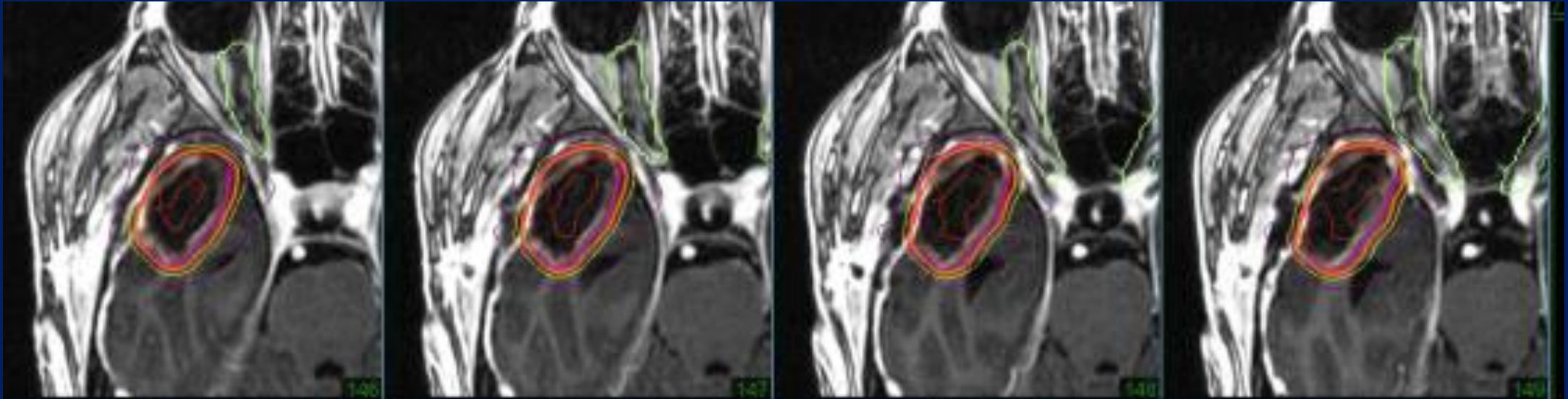
Most side effects of radiotherapy, including radiotherapy delivered with Accuray systems, are mild and temporary, often involving fatigue, nausea, and skin irritation. Side effects can be severe, however, leading to pain, alterations in normal body functions (for example, urinary or salivary function), deterioration of quality of life, permanent injury and even death. Side effects can occur during or shortly after radiation treatment or in the months and years following radiation. The nature and severity of side effects depend on many factors, including the size and location of the treated tumor, the treatment technique (for example, the radiation dose), the patient's general medical condition, to name a few. For more details about the side effects of your radiation therapy, and if treatment with an Accuray product is right for you, ask your doctor.

# ***A CASE THAT SHOWS US WHAT WE LEARNED THROUGH THE YEARS***

It all begins in Sept 2014

- 54 yo, T3N1M1 triple negative BRCA breast cancer
  - Femur metastasis, biopsy confirmed, treated with palliative dose RT
- Complete response to neoadjuvant AC chemotherapy confirmed on bilateral mastectomy
- Chest wall and supraclavicular radiotherapy and adjuvant carboplatin/taxol

# Dec 2015, resection of solitary brain metastasis followed by stereotactic radiosurgery alone

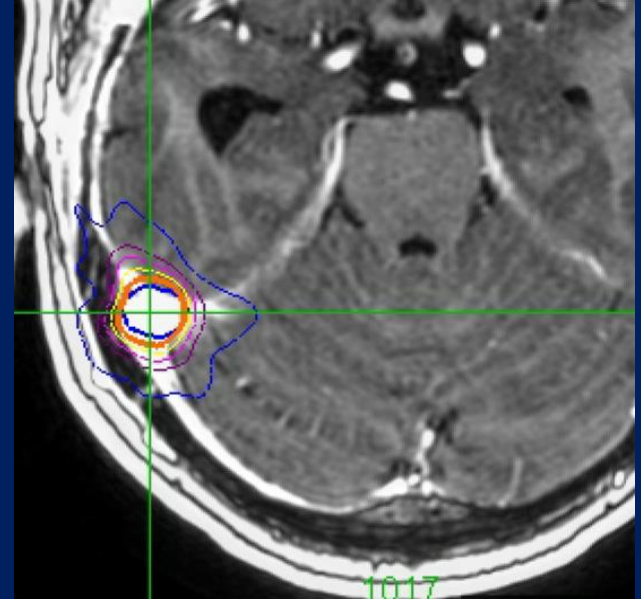
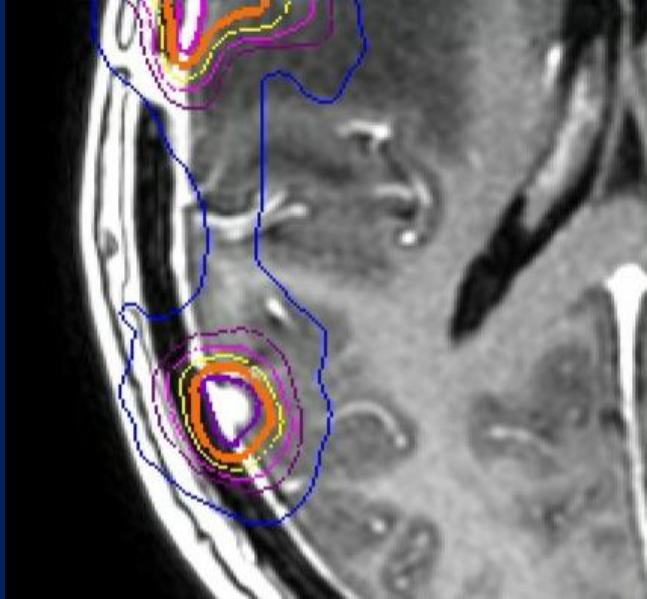
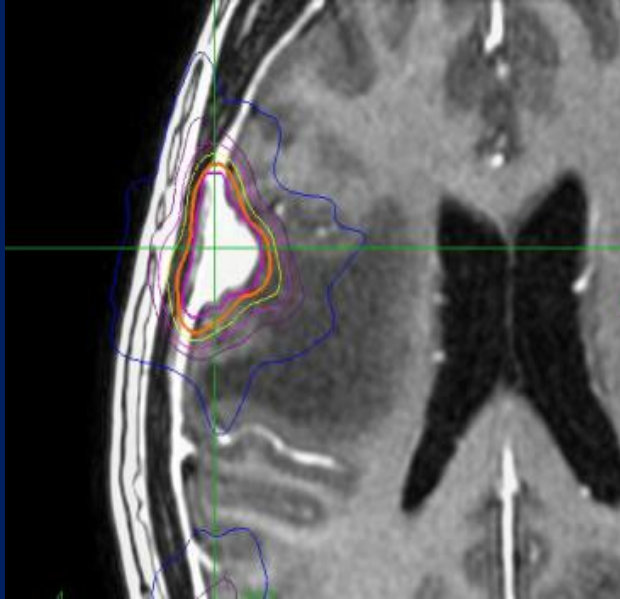


At that time this approach made “News Headlines” in 2015

*WSJ: “Study Questions Use of Whole Brain Radiation to Treat Cancer”*

*NBC News: “Brain Radiation: The Treatment is Worse Than the Illness”*

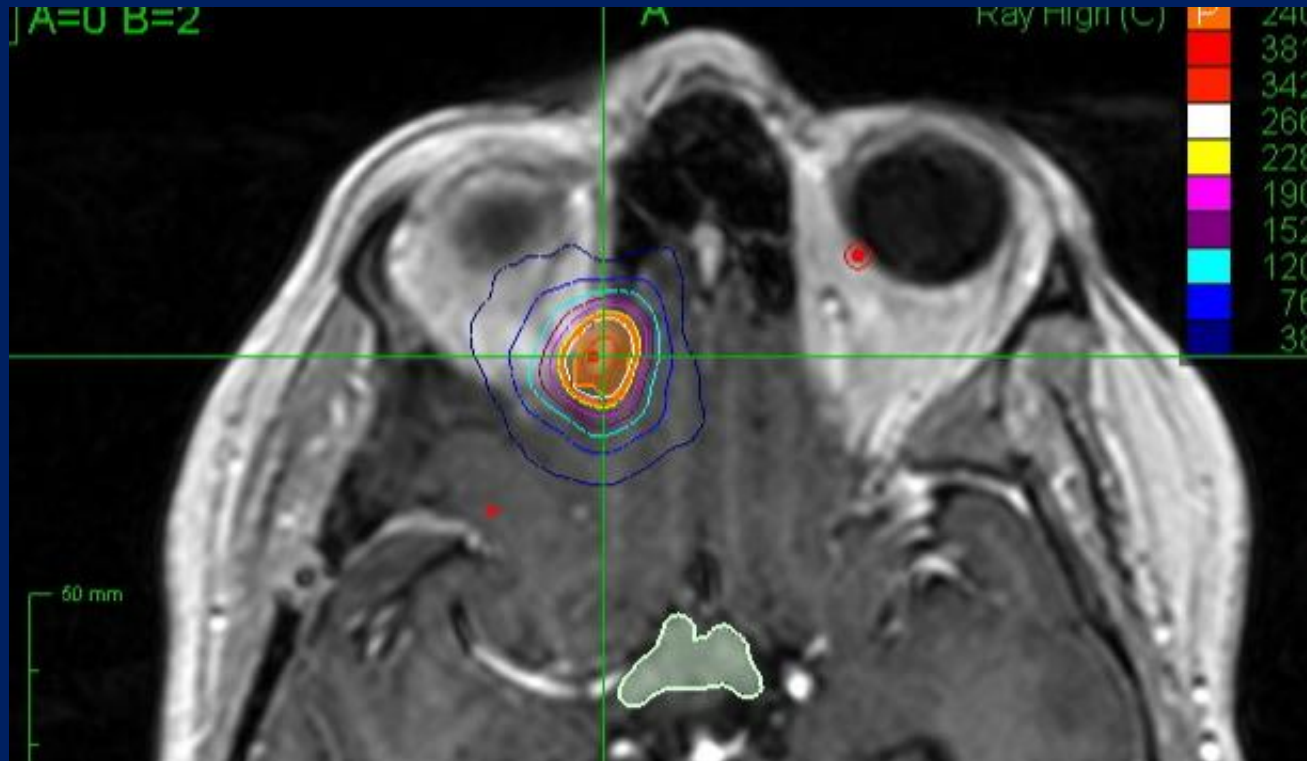
# 5 months later, 3 new dural lesions Stereotactic Radiosurgery



## Radiosurgery to new lesions after radiosurgery “failure”, rather than WBRT

- Median survival 13 months, median intracranial progression free survival 4.5 months
- Favorable prognostic factors: >6 months from prior radiosurgery, controlled extracranial disease, performance status

# Just two months later, and 7 months in... Another Brain Lesion

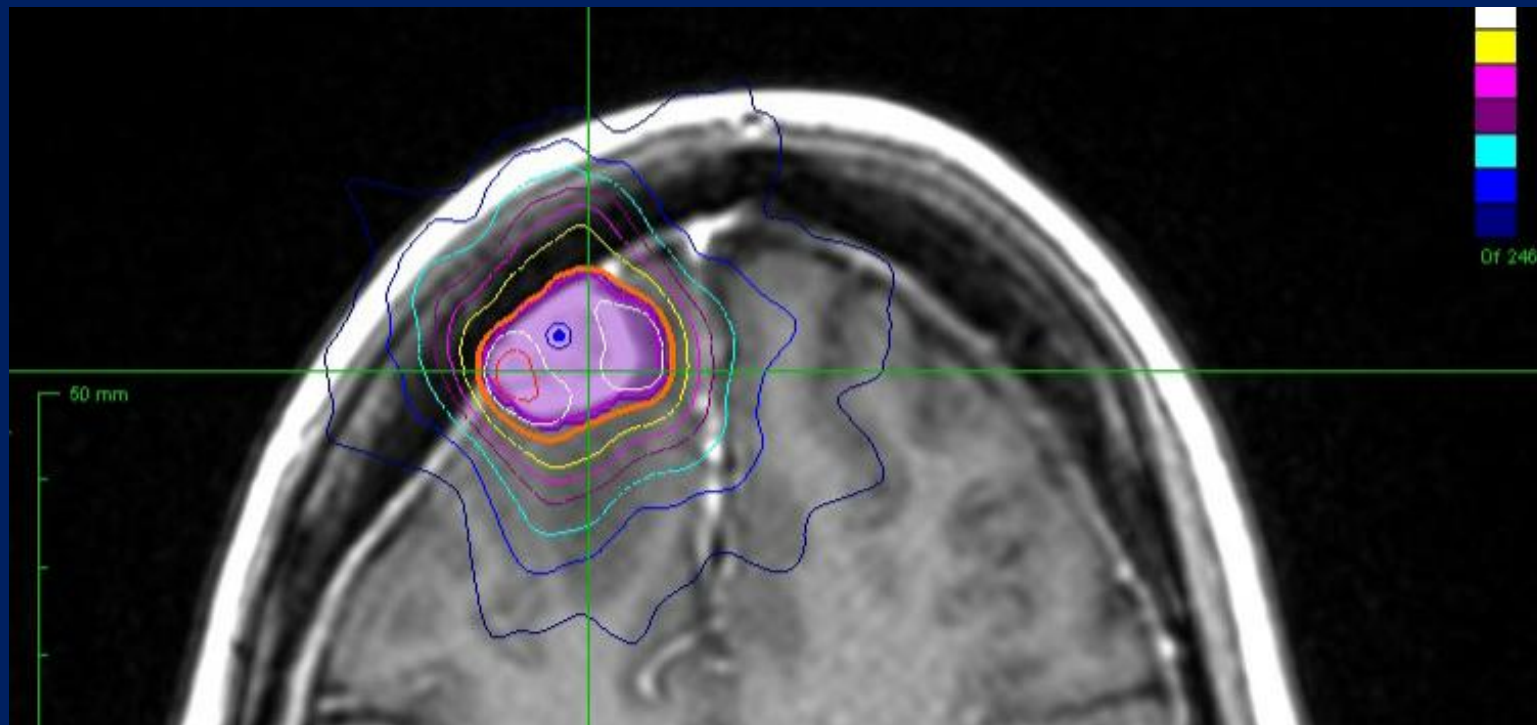


Brain Metastasis Velocity, number of new brain lesions per year at first failure after radiosurgery

Median OS for BMV < 4 was 12.5 months, **BMV 4-13 was 7.0 months**, and BMV > 13 was 4.6 months

Farris Int J Radiat Oncol Biol Phys 2017 May 1;98(1):131-141 and McTyre, Radiother Oncol 2020 Jan: 142: 168-174.

**In another 9 months, 16 months in to brain mets course...  
Still no evidence of systemic failure, but Pembrolizimab added**



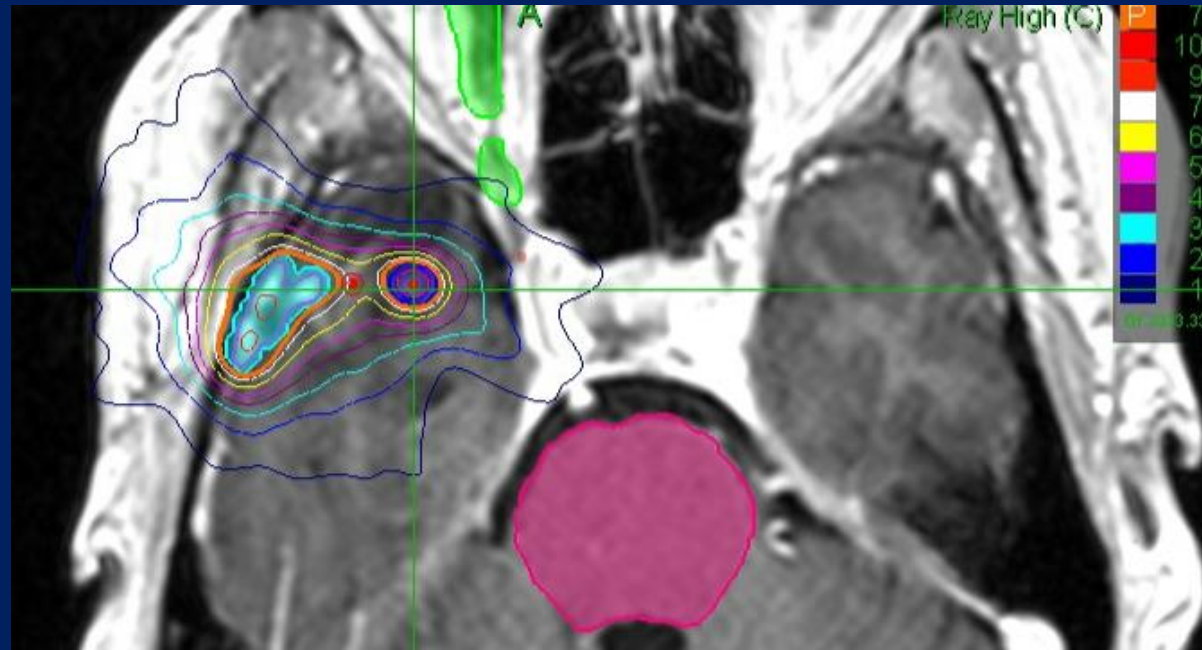
Radiosurgery Without Interruption of Systemic Therapy

Retrospective data suggests safety of radiosurgery with systemic chemotherapy, immunology drugs, and targeted agents without signal for increased radionecrosis or myelosuppression.

Shen et al, Int J Radiat Oncol Biol Phys 2016 Jun 1;95(2):735-42



**But Just three months later, and 19 months in...  
Two lesions at original radiated resection bed  
Patient selected further radiation...**



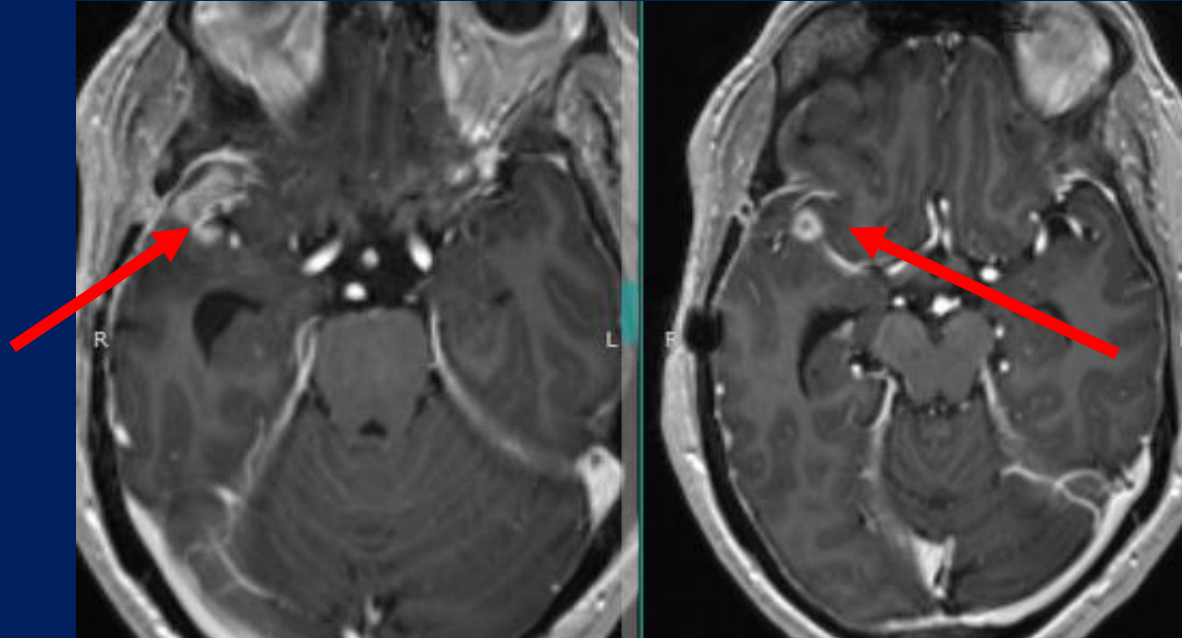
Imaging Changes: Tumor and Necrosis are Indistinguishable

Surgical Pathology of Imaging Progression: 63% Tumor and 37% pure treatment effect

An experienced blinded neuroradiologist: Sensitivity of 97%, Specificity 19% for tumor

Peng, IJROBP 102, 2018, 1236-1243

**In 3 more months..... Continued “Progression”  
Resection: *Macrophage Rich Inflammation*  
Over 2 years, 5 radiosurgeries and 2 surgeries**

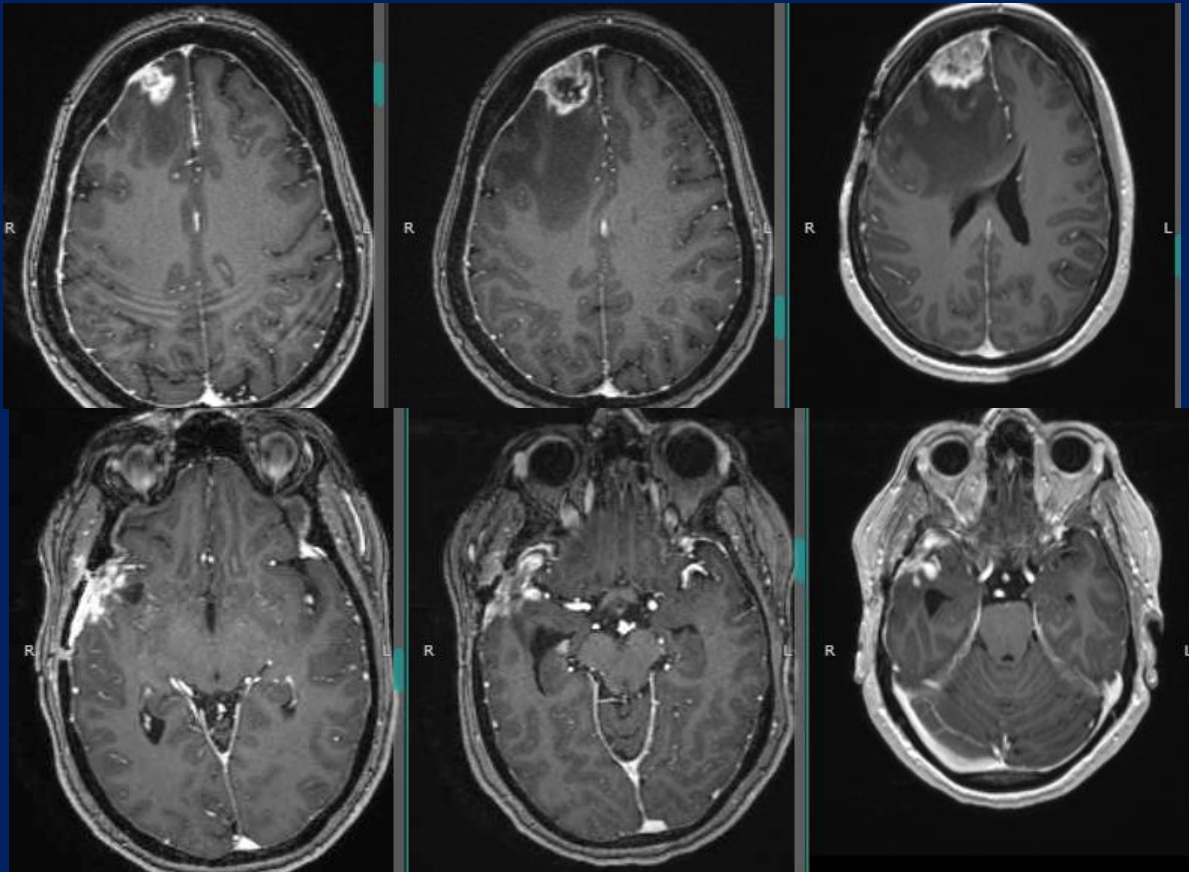


1-3) BRAIN TUMOR (RESECTION): MACROPHAGE-RICH INFLAMMATION. SEE COMMENT.

COMMENT: Fragment of gray and white matter show reactive astrocytes, highlighted on GFAP stain. Abundant macrophages are present, particularly in white matter. CD68 and CD163 demonstrate the extent of the histiocyte infiltrate. HE/LFB shows patchy areas lacking myelination.

# A peaceful 7 months (28 months in...) Two more areas of progression in Irradiated Areas Resect, Stop pembrolizumab and start Olaparib, No RT

Progression continued over 3 scans



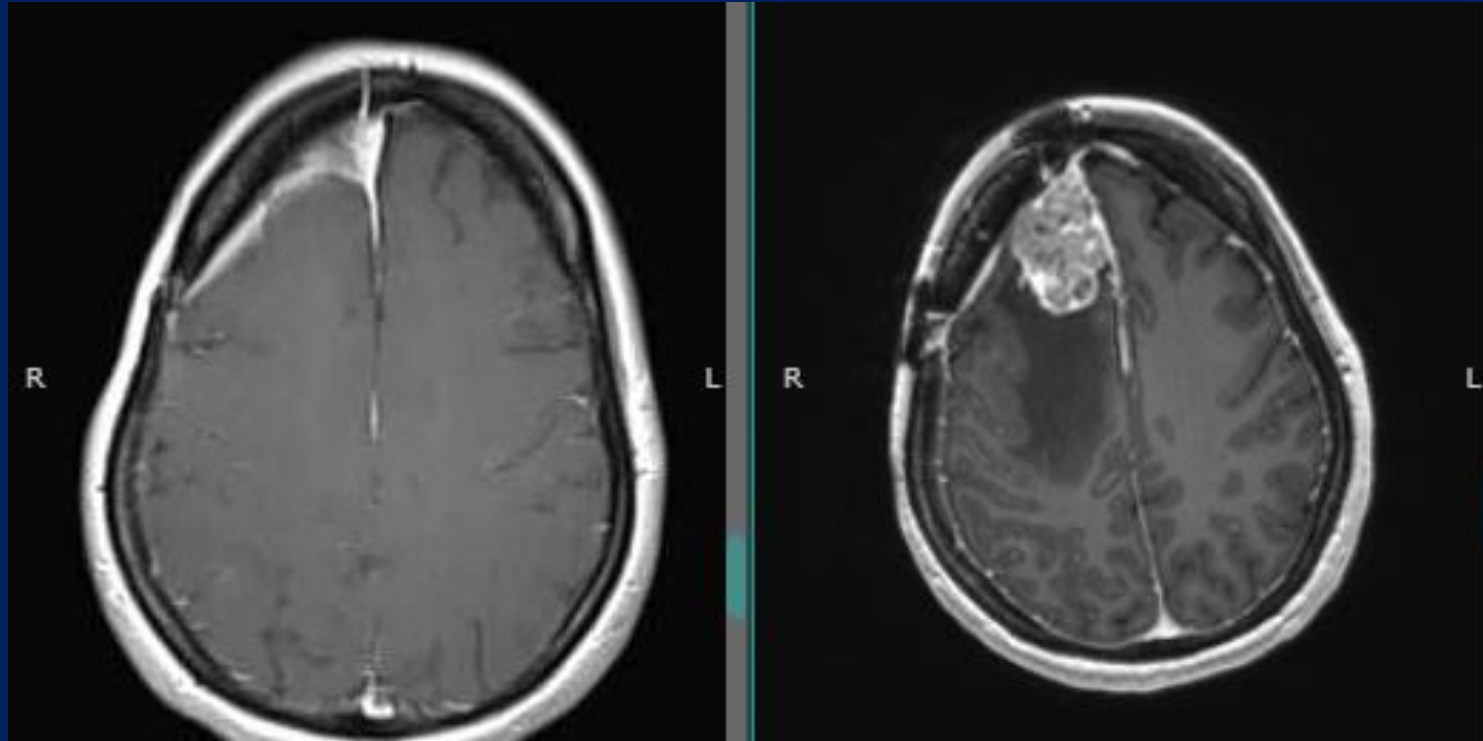
1) BRAIN TUMOR (RESECTION): METASTATIC CARCINOMA, POORLY DIFFERENTIATED WITH LARGE PLEOMORPHIC GIANT CELLS (ANAPLASTIC). SEE NOTE.

NOTE: The tumor shows numerous anaplastic tumor cells. By immunohistochemistry, tumor cells are positive for CK7, AE1/AE3, and focally positive for CK5/6. Negative markers include mammaglobin, GATA3, PAX8, TTF1, ER and PR. Ki67 proliferation rate is high (30%). Given the previous specimens from tumors in the breast and axillary lymph nodes describing a tumor with similar immunophenotype, the tumor likely represent the tumor metastasizing to brain.

2) INFERIOR RIGHT TEMPORAL (RESECTION): DIFFUSE ASTROCYTOMA (WHO II). SEE NOTE.

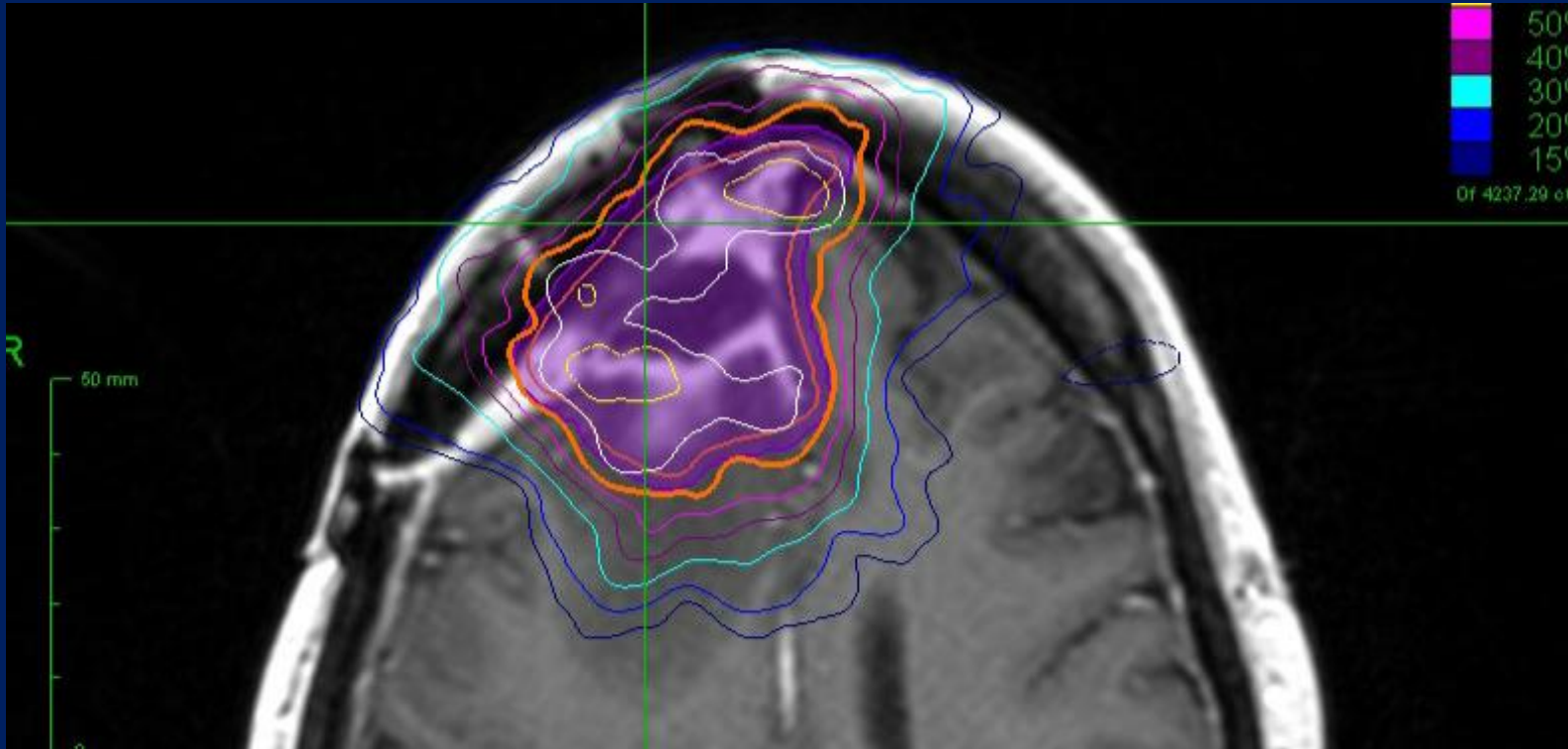
NOTE: By immunohistochemistry, the tumor is positive for OLIG2, and ATRX is retained. P53, and IDH are negative. Ki67 is low. Molecular testing was requested and will be reported separately in EPIC when available.

**9 months after resection alone, 3 years in by now...  
Progression in Irradiated Frontal Area  
Repeat resection selected**



1) BRAIN, TUMOR (RESECTION): METASTATIC POORLY DIFFERENTIATED CARCINOMA WITH ANAPLASTIC FEATURES, SEE NOTE.

# This time Repeat Radiosurgery administered

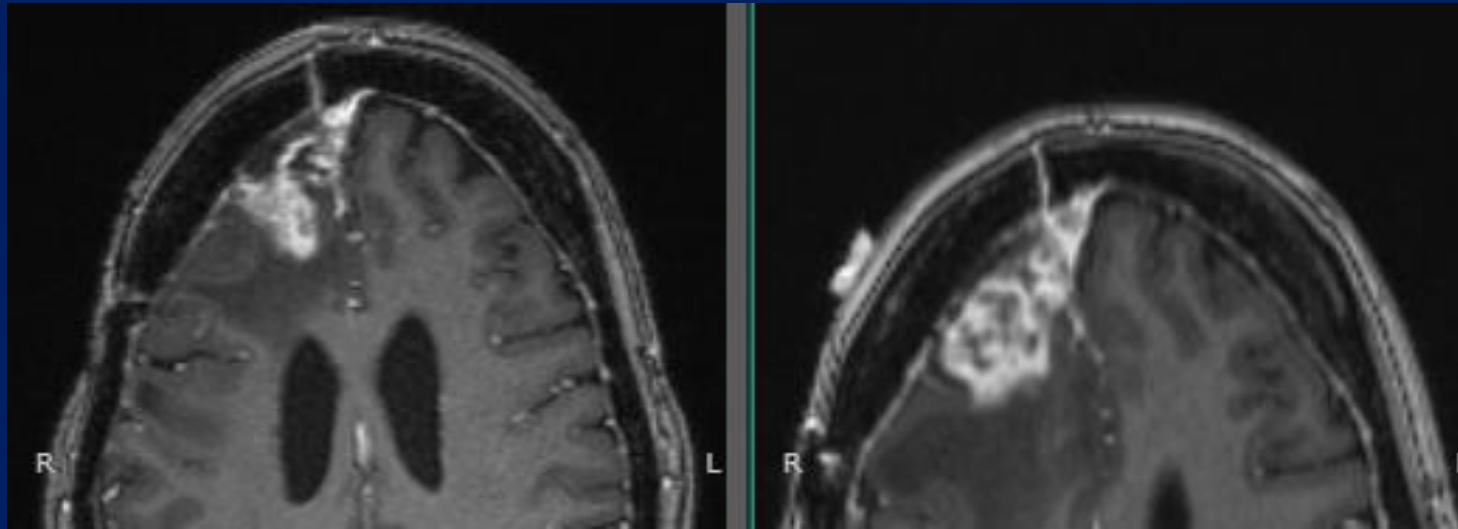


## Results of Resection Followed by Repeat Radiosurgery

- Local control at 2 years 79.5% (95% CI 68.3-92.5%)
- Necrosis: 9% after resection and repeat radiosurgery

Bhattia , in press Neurosurgery Practice

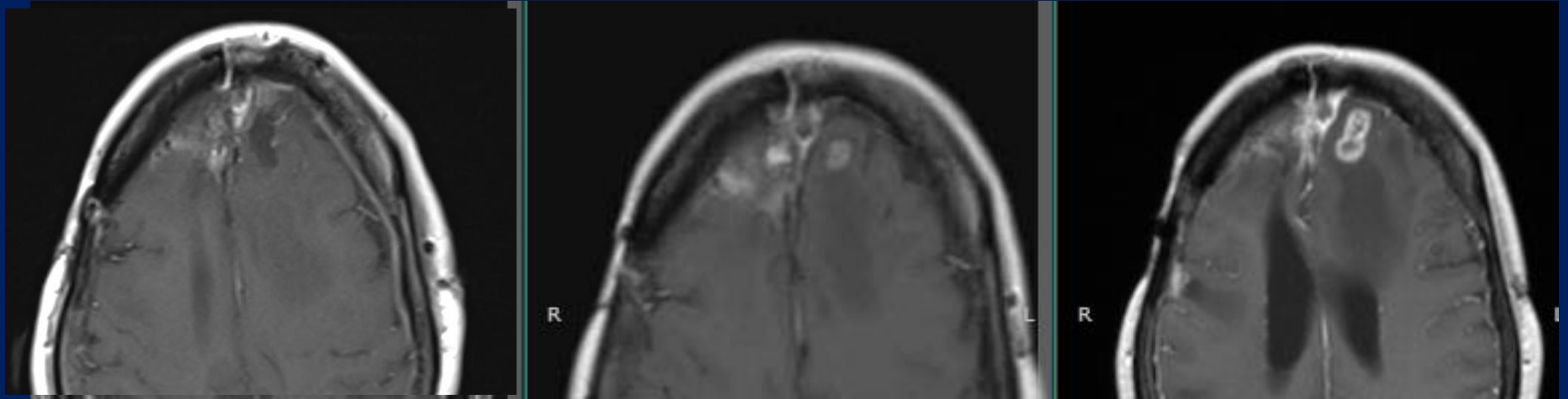
**21 months of control (the sixth year) until.....  
Progression again in aame Frontal Area  
Resected and no additional RT given 2 prior course**



**1,3. Brain Tumor, Anterior Perimedial, Right (Resection):**  
Metastatic poorly differentiated carcinoma. See note.

NOTE: The patient's history of metastatic breast carcinoma to the brain is noted. Immunohistochemistry performed on block 3A demonstrates the neoplastic cells are positive for AE1/AE3, and are negative for ER (0%) and PR (<1%, weak). The findings in parts 1 and 3 are compatible with metastasis from the patient's known breast carcinoma.

**In 11 months, Progression in contralateral area that appeared to only get a modest radiation dose before**

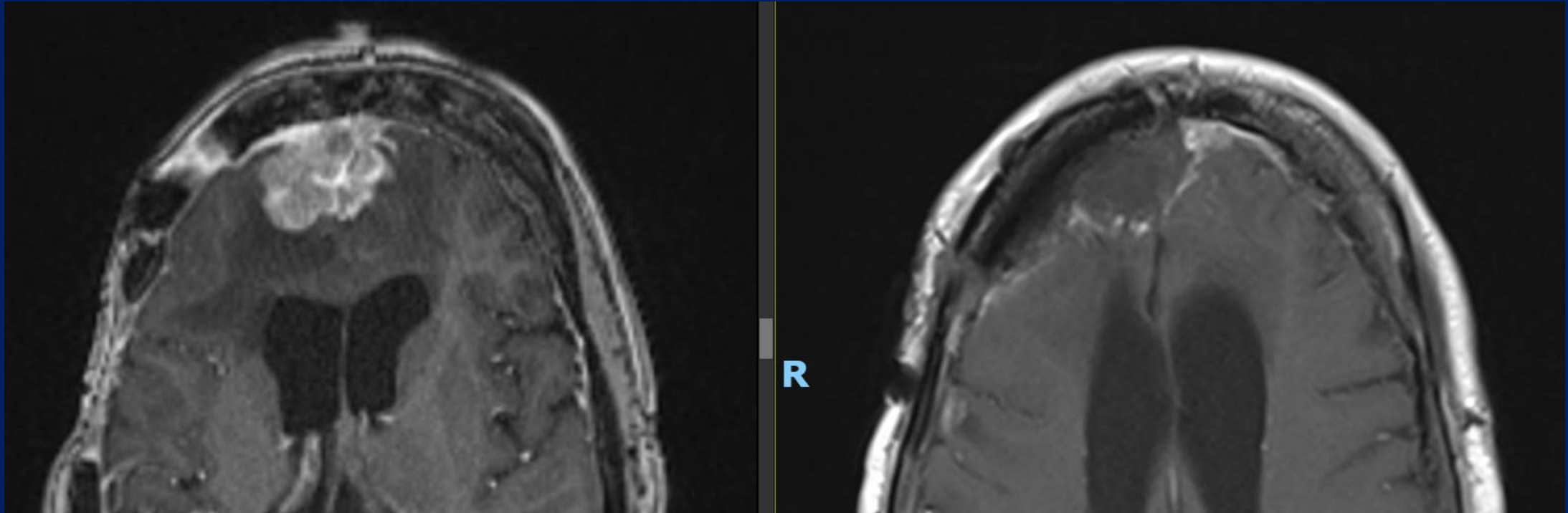


**Diagnosis**

1. Brain, Frozen (Biopsy): Predominantly treatment related changes with gliosis, Negative for metastatic carcinoma (see note)
2. Brain, Anterior Nodule (Biopsy): Predominantly treatment related changes with gliosis, Negative for metastatic carcinoma (see note)
3. Brain, Mass (Biopsy): Predominantly treatment related changes with gliosis, Negative for metastatic carcinoma (see note)

**Still excellent function, excellent cognition, retired at age 62 from professional career,  
No systemic recurrence in 7 years since first diagnosis of metastatic cancer**

# But then in 16 more months (99 since first brain me) Recurrence again, resection, and observation...



1-3.Brain, Brain Tumor (resection): Metastatic poorly differentiated carcinoma. See note.

Note: The patient's history of metastatic breast carcinoma and diffuse astrocytoma, IDH-wildtype (S18-26921) status post multiple resections and radiation therapy is noted. The current tumor is consistent with a metastatic breast carcinoma.

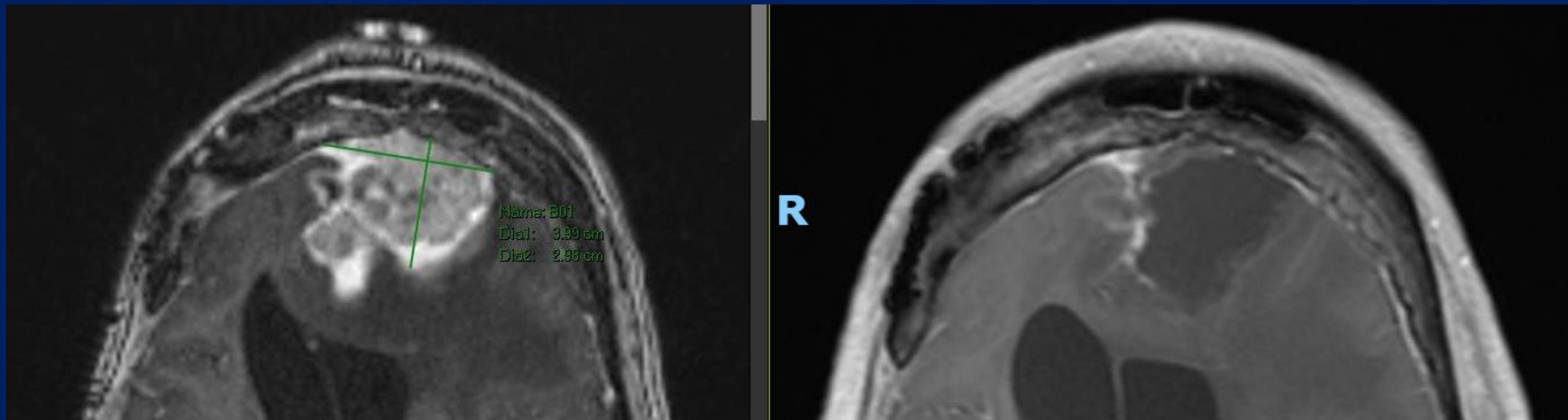


But in only another 5 months (9 years in...)

Resection of rapid progression

**What should we do now?**

*Radiosurgery 6 years and 4 years earlier, Olaparib for 5 years*



**Left intradural tumor (Resection):**

Metastatic carcinoma, compatible with the patient's known breast primary. See note.

# In a few months, 10 years since first brain metastasis

7 neurosurgeries, 6 courses of robotic stereotactic radiosurgery  
Good quality of life, lives independently, good cognitive function,  
no other systemic recurrence

*Let's make an agreement:*

We meet again at **ASTRO  
2034** to go over her next 10  
years!



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