



Multidisciplinary Approaches to Cancer Symposium

Tumor Board: Management of Brain Metastases

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Panel & Disclosures

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- *No relevant financial relationships*

- *Consultant for AstraZeneca, Dava Oncology, & Ideology Health; On the Speakers Bureau for MJH Life Sciences; Stock/Shareholder (publicly owned companies) Actuate Therapeutics, ArriVent BioPharma, BEAM Therapeutics, BeOne Medicines, Immunitybio, Legend Biotech, Elicio Therapeutics, Immuneering Corporation, Kymera Therapeutics, Revolution Medicine, Summit Therapeutics, Takeda, Tango Therapeutics, & Zai Biopharmaceutical*

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This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

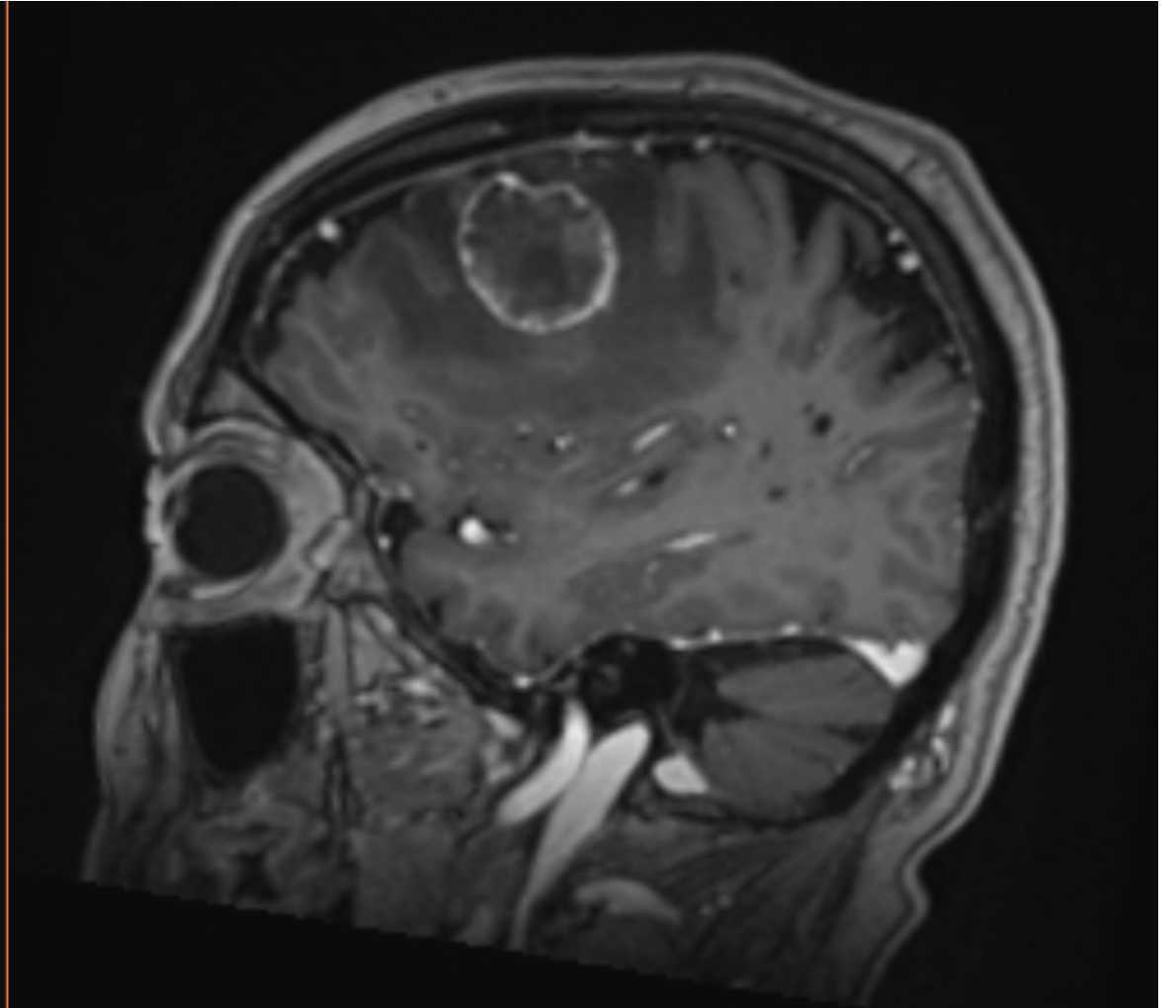
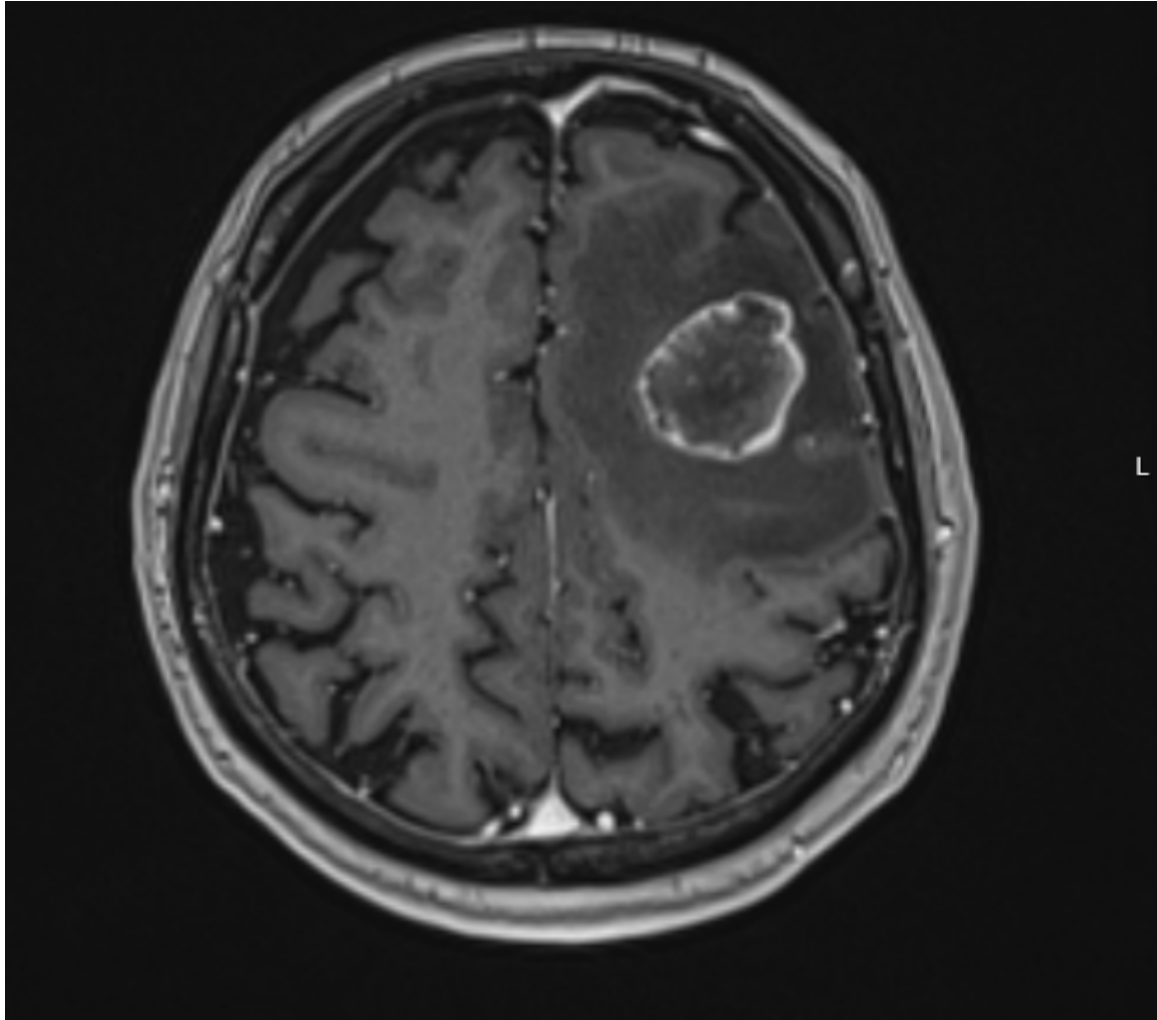
- *The presentation will address how language, health literacy, cultural beliefs, caregiver support, socioeconomic status, transportation access, and insurance coverage can affect decision-making and treatment adherence for patients with brain metastases. We will discuss how patients may differ in their understanding of prognosis, goals of care, surgery, radiation, systemic therapy, clinical trials, and end-of-life planning, and how clinicians can use interpreters, plain-language counseling, shared decision-making, and culturally sensitive communication to support equitable care.*
- *The presentation will address how implicit bias may influence which patients are offered neurosurgical evaluation, stereotactic radiosurgery, systemic therapy, clinical trials, rehabilitation, palliative care, or aggressive multimodality treatment. We will discuss how assumptions about age, functional status, social support, race/ethnicity, language, insurance status, disability, or perceived adherence may affect treatment recommendations, and how a structured multidisciplinary tumor board approach can help reduce bias and promote consistent, evidence-based management.*

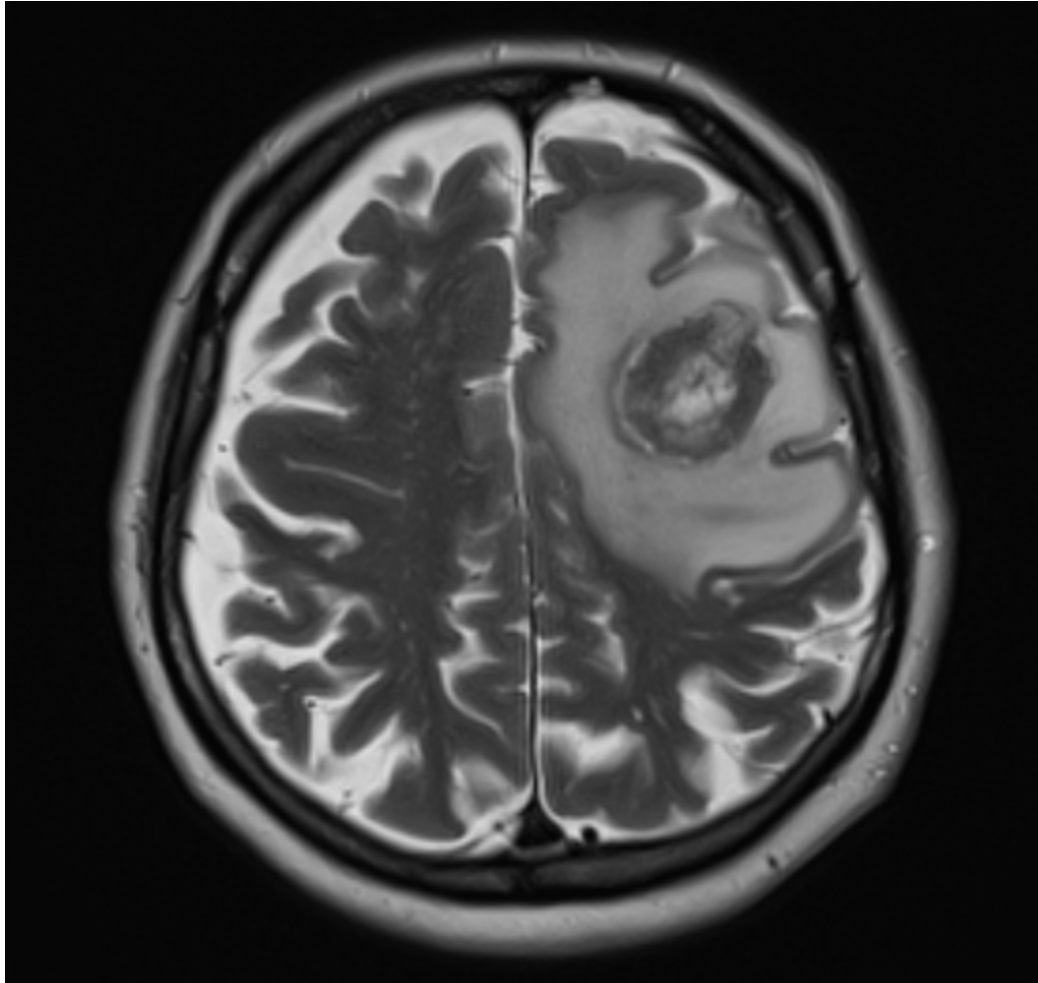


Patient 1:

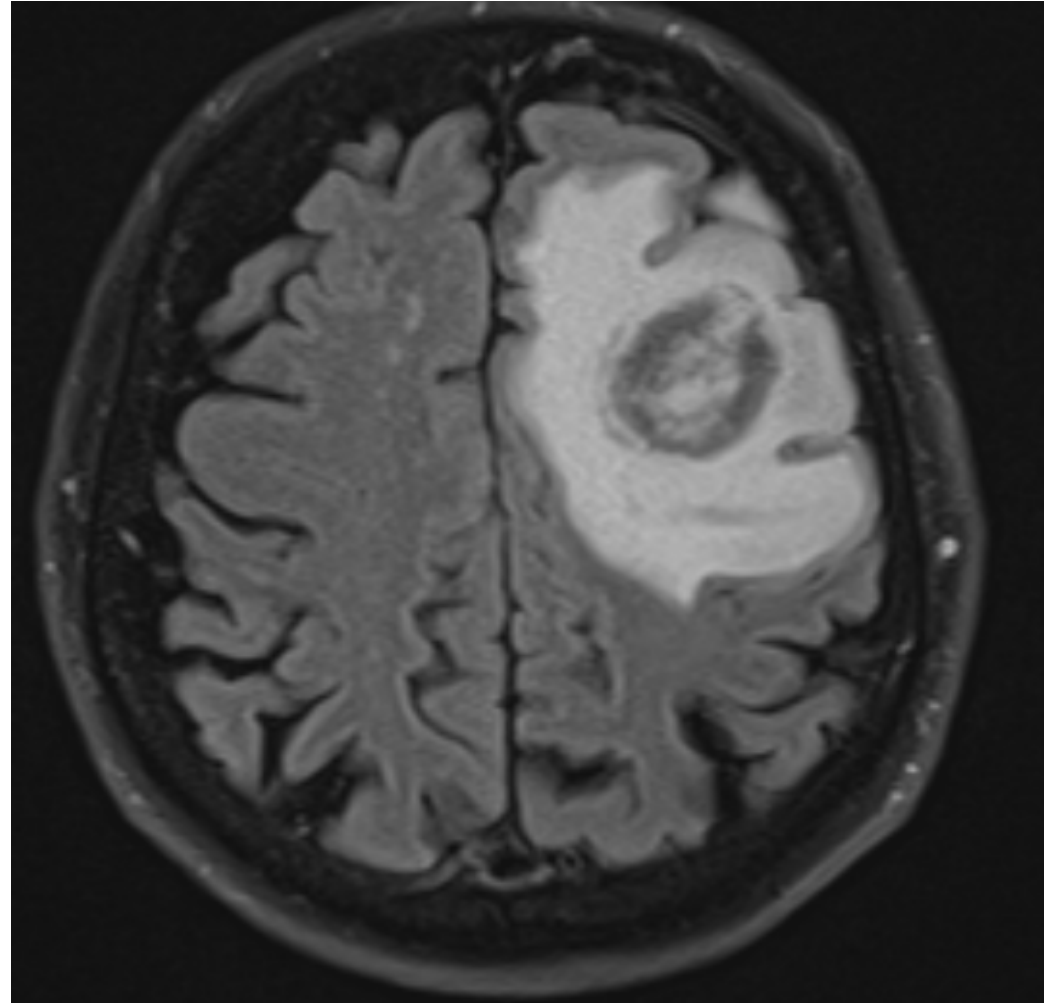
- 74 y.o. male with a history HTN, cholecystitis, prostate adenocarcinoma Gleason score 7 s/p Relugolix 4/2/205 and radiation therapy completed 7/2025 with undetectable PSA.
- Presented with one month of expressive aphasia, word finding difficulty, confusion, memory and gait instability.
- No headaches, nausea or vomiting
- Exam: Oriented to person, place and time. CN II-XII intact and equal. Speech slow, with word finding difficulties, equal strength in BUE and BLE, normal finger-to-nose







Axial T2



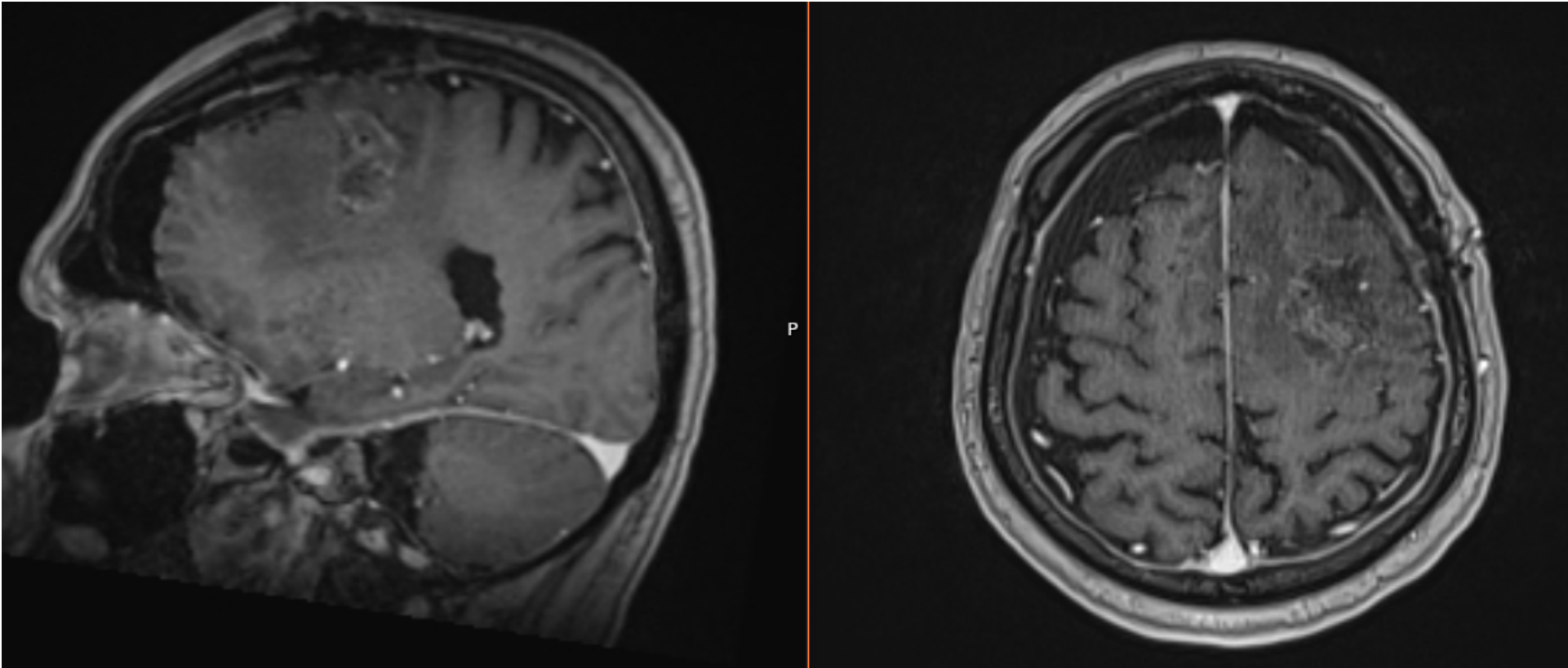
Flair

Initial medical management:

- IV dexamethasone: 10mg once, followed by 4q6, protonix, insulin sliding scale
- No evidence of seizures, therefore, no AEDs
- Speech improved within 24 hours

Surgical management:

- Stealth navigation assisted left frontal craniotomy for tumor resection



- Rapid dexamethasone wean, post operative keppra

Pathology report

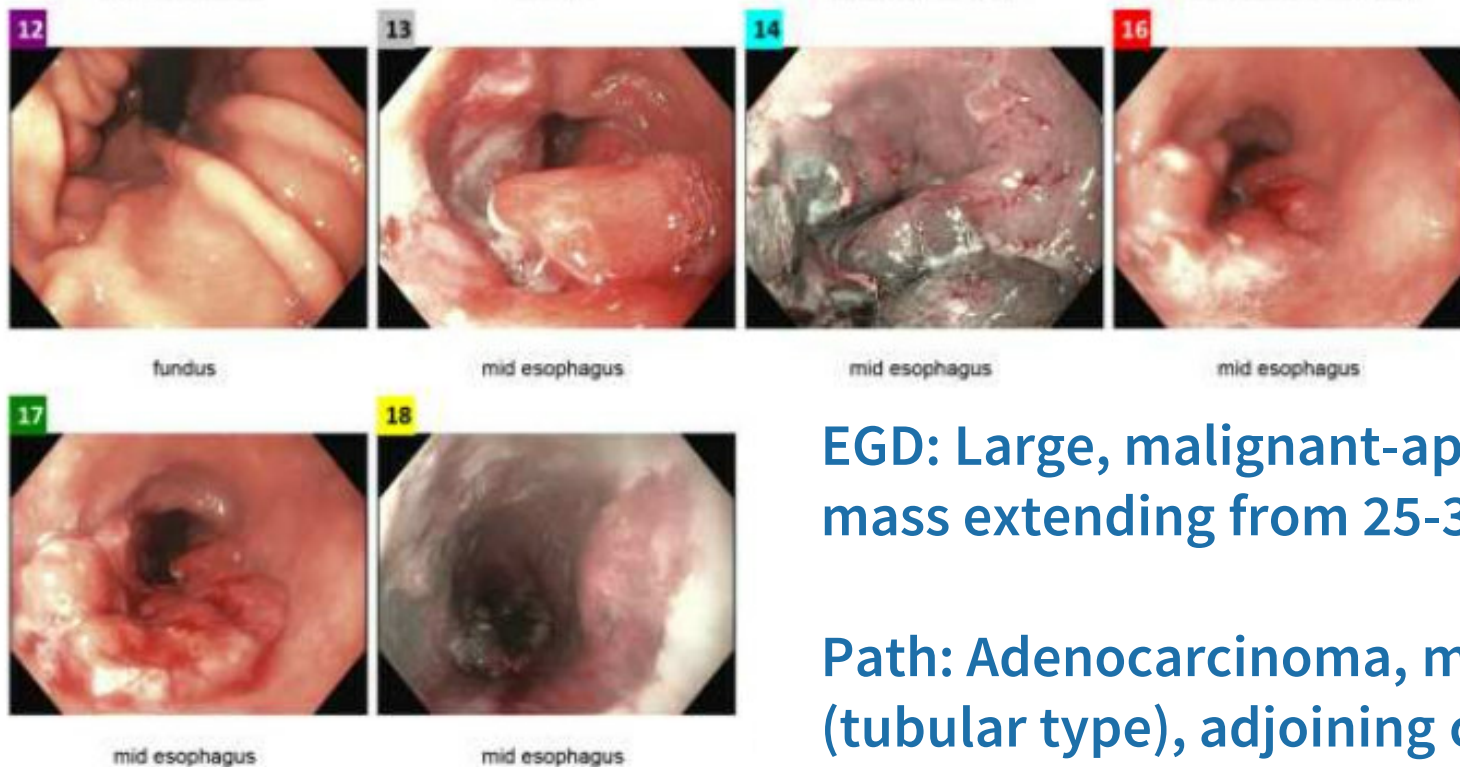
Sections demonstrate a high-grade metastatic carcinoma. The viable tumor shows a high proliferative index (Ki-67 approximately 50%). The tumor is positive for AE1/AE3 and CK7, with variable expression of CK20 and CDX2. SATB2 is negative. The tumor is negative for TTF-1, GATA3, p63, and synaptophysin. The patient's history of prostate carcinoma is noted; however, the tumor is negative for NKX3.1 and PSA, providing no immunohistochemical support for prostatic origin.

Overall, the morphologic and immunohistochemical findings favor metastatic carcinoma of gastrointestinal origin. The immunophenotype is not specific for a particular gastrointestinal primary site. Clinical and radiographic correlation, including evaluation of the gastrointestinal tract, is recommended.



Further work-up

- Last colonoscopy was 2 months earlier, noted to have 3mm polyp removed
- While still in patient, a bidirectional endoscopy was performed to identify occult primary



EGD: Large, malignant-appearing mid-to-distal esophageal mass extending from 25-32 cm from the incisors

Path: Adenocarcinoma, moderately to poorly differentiated (tubular type), adjoining cardiac type mucosa with intestinal metaplasia; claudin 18 +; HER-2 3+

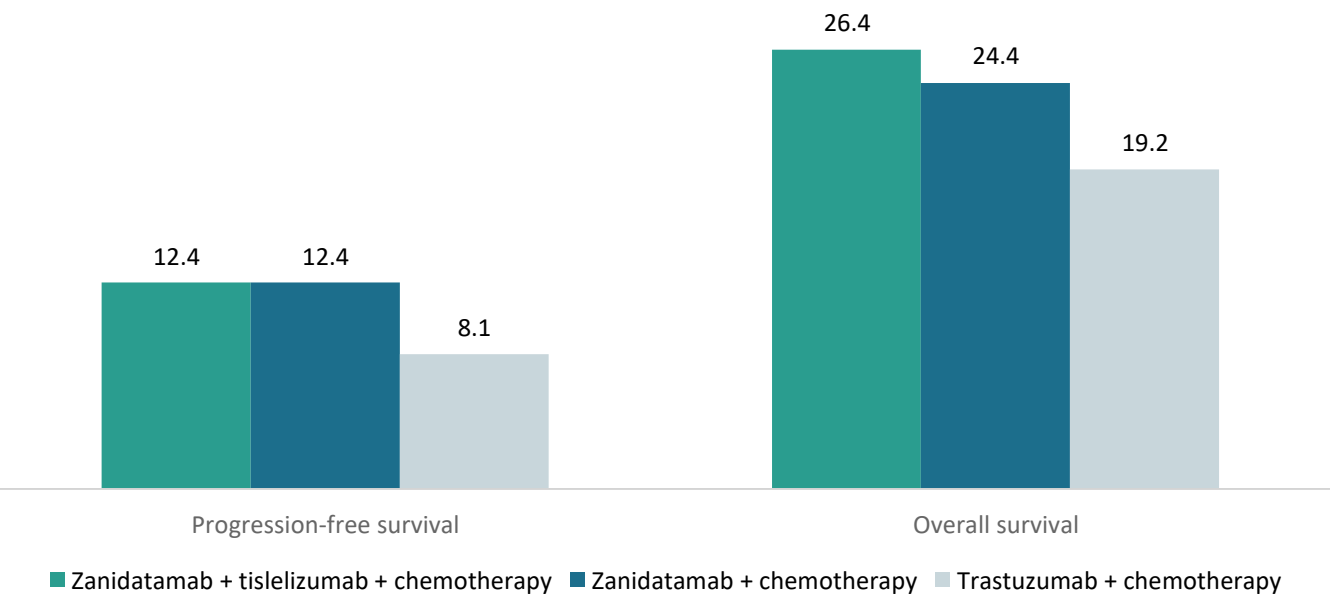
2yr OS > 73.5%, systemic treatment is HER2-directed therapy



HERIZON-GEA-01 changed first-line HER2-positive GEA treatment

Phase 3, n=914 | Unresectable locally advanced or metastatic gastric, GEJ, or esophageal adenocarcinoma

Median efficacy outcomes



24-month overall survival



FDA approval

August 25, 2026

For HER2 IHC 3+ disease

Zanidatamab + fluoropyrimidine/platinum chemotherapy

OR

Zanidatamab + tislelizumab + fluoropyrimidine/platinum chemotherapy

The triplet also covers IHC 2+/ISH+ tumors.

Key safety issues

Diarrhea, infusion reactions, and left ventricular dysfunction require proactive monitoring.



CNS activity remains unproven

HERIZON-GEA-01 supports systemic efficacy, but it does not establish blood-brain barrier penetration or intracranial benefit

No prospective CNS response, CNS-PFS, CSF pharmacokinetic, or brain-to-plasma exposure data were reported.

Who could enroll

Stable, treated brain metastases

Patients had to be neurologically stable, off steroids and anticonvulsants, with no radiographic progression for at least 4 weeks.

Who was excluded

Untreated or symptomatic CNS disease

The trial excluded recent CNS radiation and known leptomeningeal disease. These criteria limit any inference about active brain metastases or LMD.

Clinical interpretation

For a patient without CNS involvement, the study directly supports systemic treatment selection when the FDA indication applies. It should not be presented as evidence that zanidatamab prevents or treats CNS metastases.



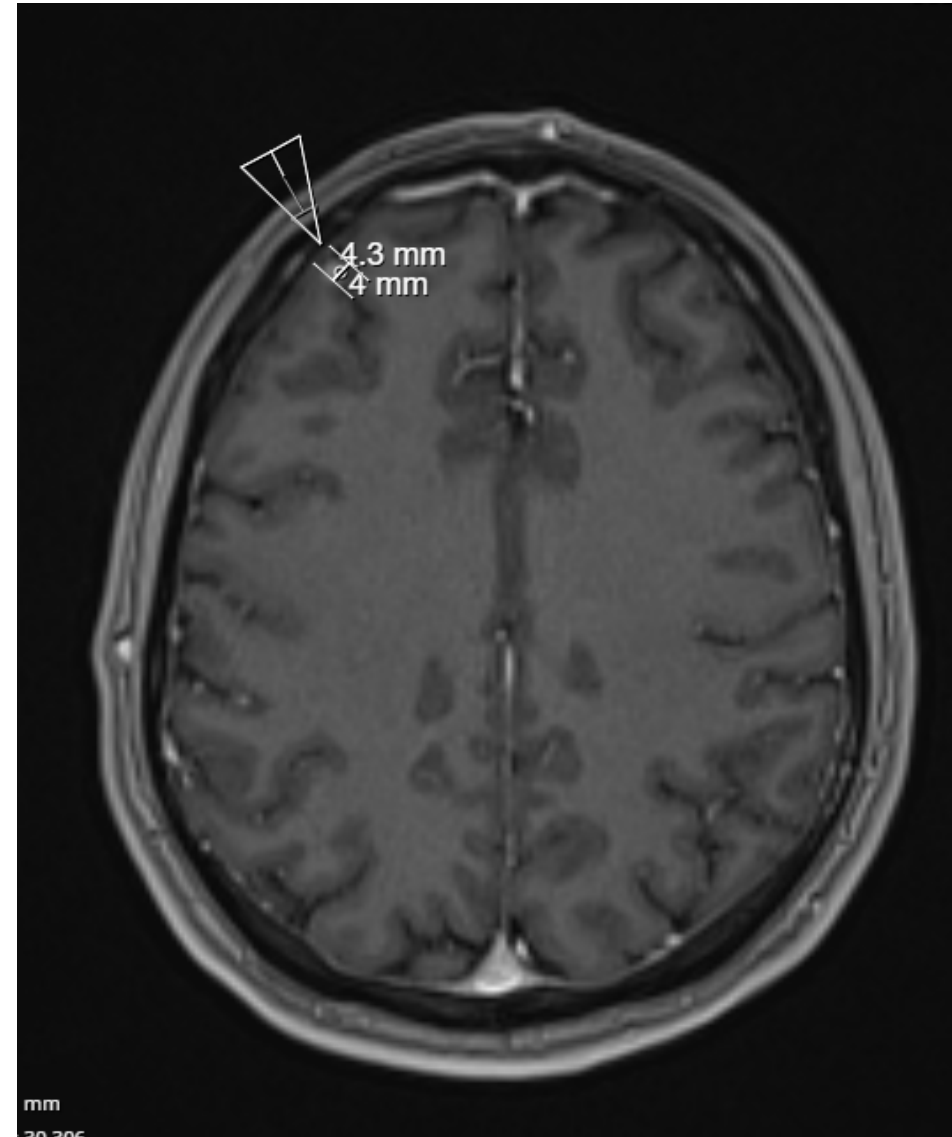
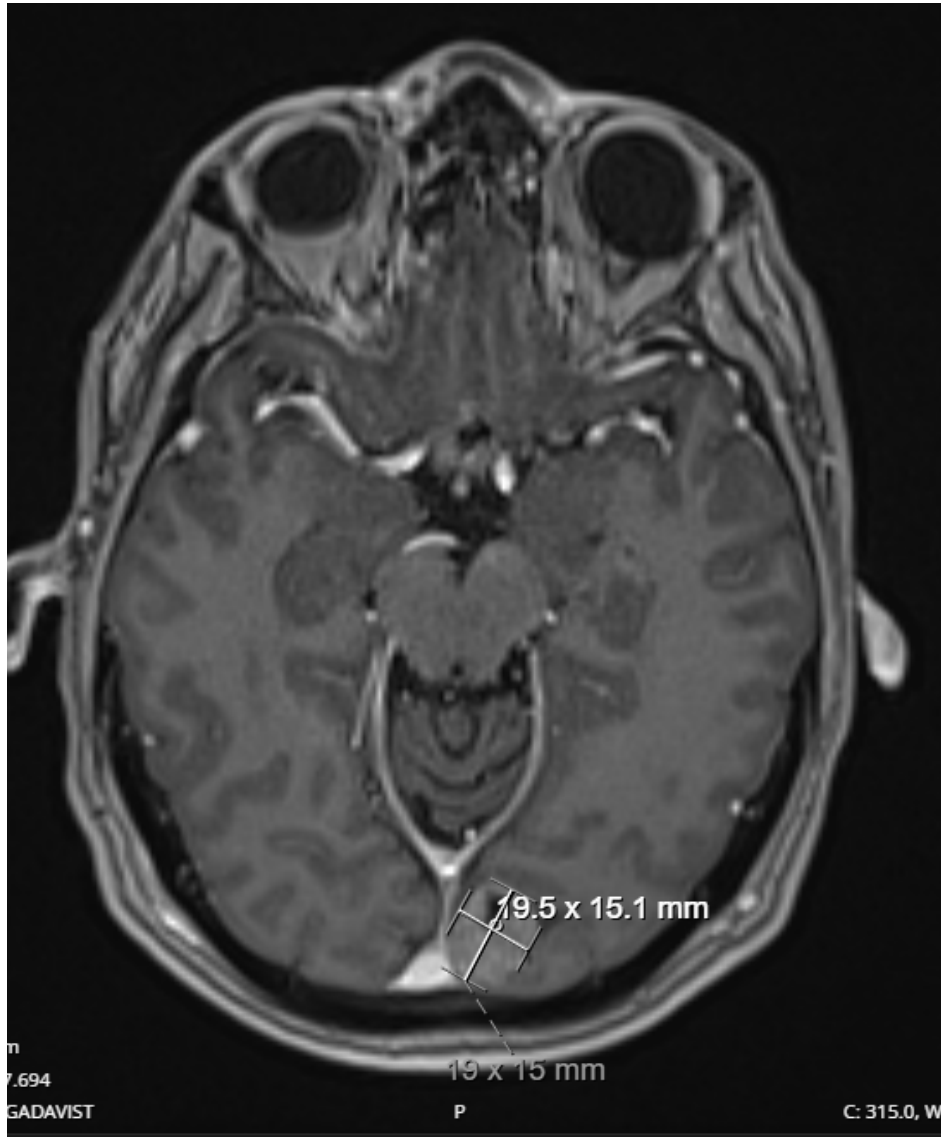
Further treatment

- Discharged to ARU
- 2 weeks following surgery, SRS to left frontal surgical bed
- Serial surveillance MRI q 3months

Patient 2:

- 57 y.o. male with a long h/o oligometastatic head and neck cancer (originally s/p definitive therapy in 2020 with subsequent targeted radiation courses to small sites of bony metastases)
- Presented with one month h/o subtle vision change
- No headaches, nausea or vomiting
- Exam: Oriented to person, place and time. CN II-XII intact and equal. Speech wnl, 5/5 strength in BUE and BLE, normal finger-to-nose, no visual field cuts



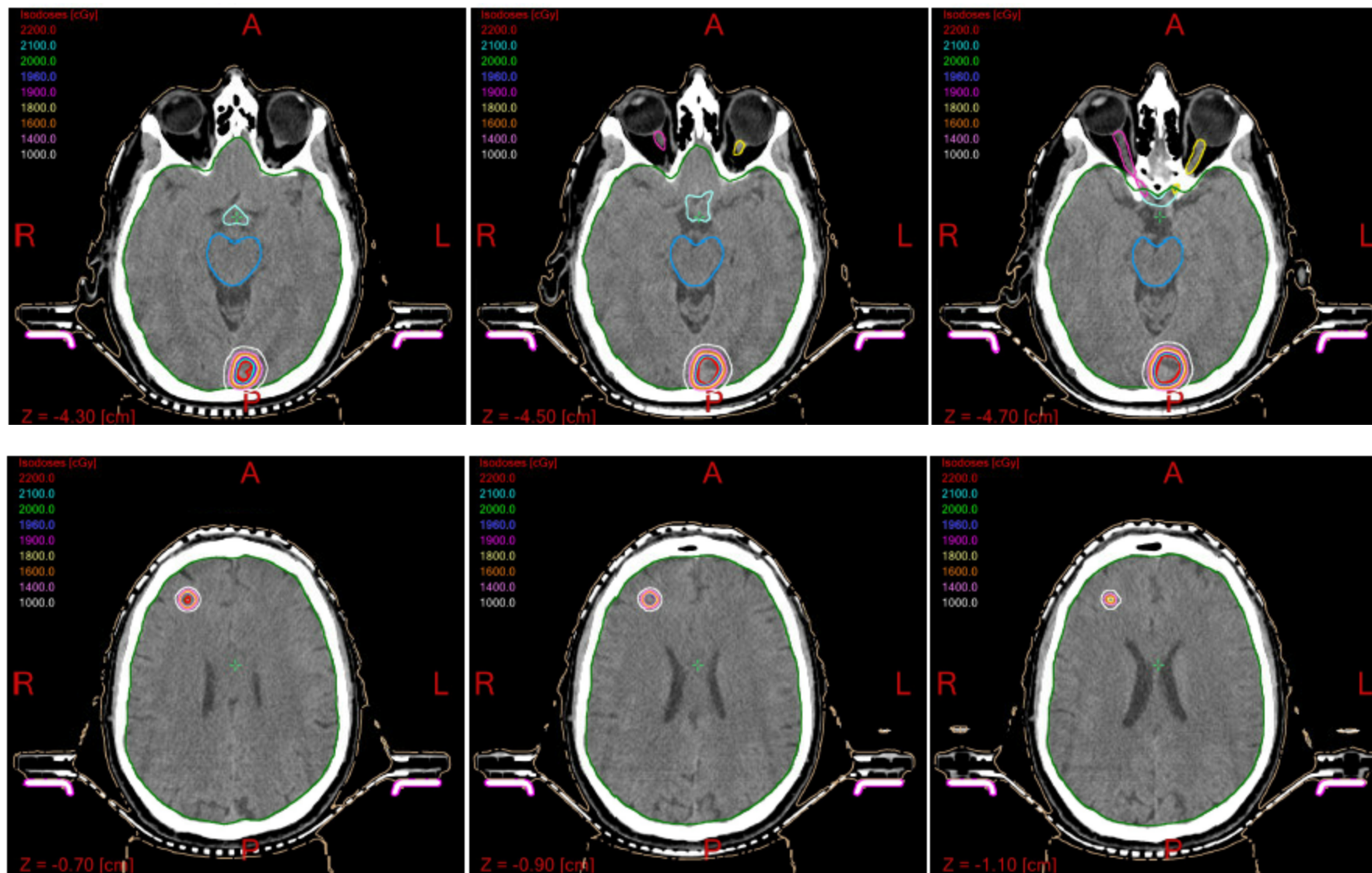


T1 post contrast

Initial medical management:

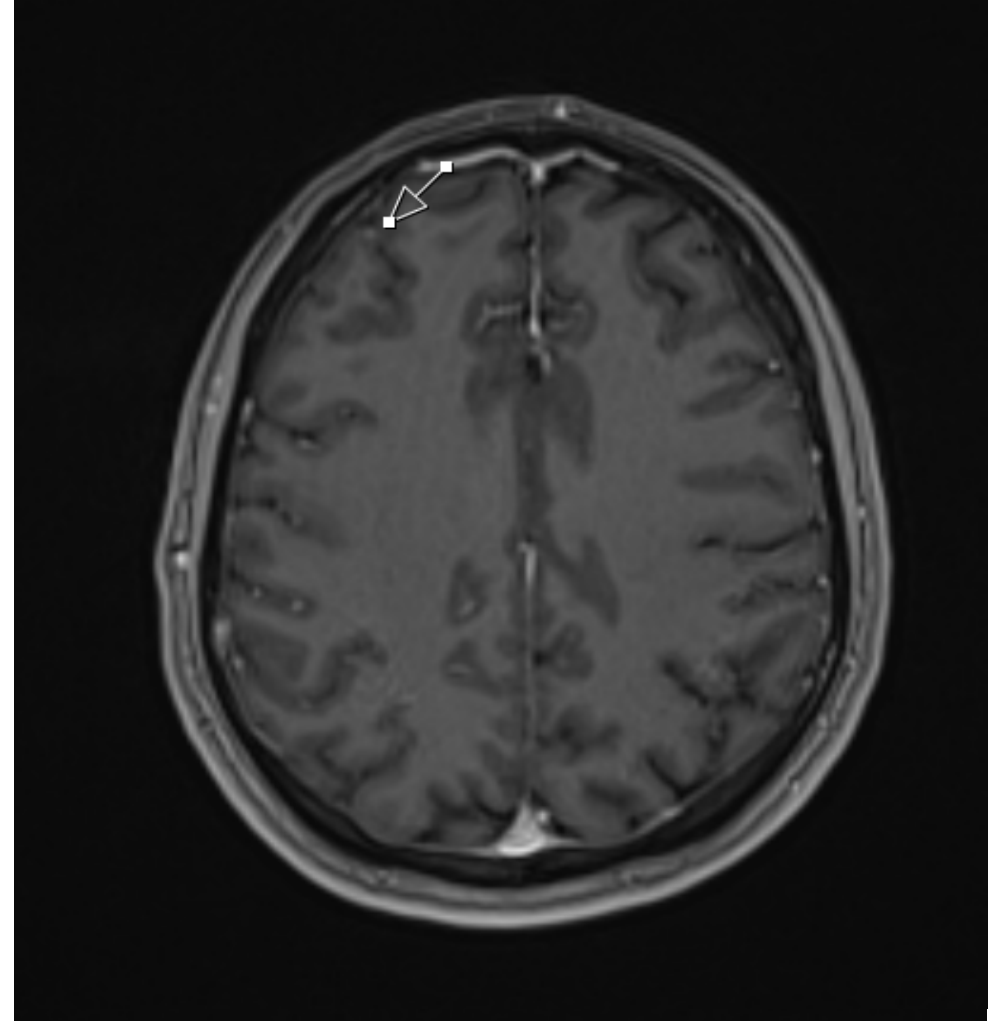
- 3 days of low dose dexamethasone

Radiosurgical management:



Outcome:

- One week after low dose dexamethasone/SRS his visual symptoms resolved
- No sequelae of therapy
- 3 Month follow up MRI:



Radiation for Brain Metastases:



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[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

CLINICAL PRESENTATION

TREATMENT^{f,g}

Newly diagnosed or
stable systemic
disease or
Reasonable systemic
treatment options
exist^{g,h}

SRS (preferred)^{i,j,k}
or
Surgical resection for management of mass effect or
symptoms followed by SRS ([BRAIN-C](#)) to the surgical
bed and other brain metastases
or
Systemic therapy in select patients^{f,g,h}
or
Hippocampal avoidance with WBRT (HA-WBRT)^{i,l,m} +
memantine

Disseminated
systemic disease
with poor systemic
treatment options^h

HA-WBRT^{f,i} + memantine^m
or
SRS^{i,k}
or
WBRTⁱ without HA ± memantine
or
Consider palliative/best supportive care

Follow-up
and
Recurrence
([LTD-3](#))



Radiation for Brain Metastases:



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NCCN Guidelines Version 3.2026 Central Nervous System Cancers

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Brain Metastases

- SRS is generally preferred over WBRT for limited brain metastases.
- SRS treatment planning MRI with thick 1-mm slice T1+c sequence is recommended and should be obtained within 14 days of initiation of SRS.⁴²
 - ▶ Maximum marginal doses from 15–24 Gy based on tumor volume is recommended.^{43–46}
 - ◊ Consider fractionated SRS for brain tumor >2 cm and/or for situations where a single-fraction SRS plan exceeds normal tissue constraints (eg, V12 brain [volume of normal brain plus target volumes receiving 12 Gy] of >10 cm).⁴⁷
 - Most common multi-fraction SRS doses include: 27 Gy in 3 fractions and 30 Gy in 5 fractions.
 - ◊ Consider preoperative SRS in select cases when logistically feasible to potentially decrease risk of post-treatment meningeal recurrence (category 2B).
 - ◊ Postoperative single multi-fraction SRS: Local recurrence rates after brain metastasis resections remain high (in the range of 50% at 1–2 years) even in the setting of a radiographic gross total resection. Postoperative SRS to the surgical cavity is supported by randomized data to improve local control over observation and to offer similar overall survival and superior cognitive preservation to postoperative WBRT.^{48,49} A consensus statement regarding radiation target delineation has been published.⁵⁰ Multi-fraction SRS may be preferred for larger cavities.⁵¹ Common dose-fractionation schedules include 16–20 Gy in 1 fraction, 24–27 Gy in 3 fractions, and 30 Gy in 5 fractions.
- SRS plus TTF is recommended in patients with NSCLC without targetable mutations.
- WBRT: Standard doses include 30 Gy in 10 fractions and 20 Gy in 5 fractions. WBRT can be done with or without HA + memantine. HA-WBRT (plus memantine) 30 Gy in 10 fractions is preferred for patients with a better prognosis (≥4 months) and no metastases within 5 mm of the hippocampi.⁵²
 - ▶ For patients with poor predicted prognosis and with symptomatic brain metastases, standard WBRT of 20 Gy in 5 fractions is a reasonable option.⁵³ If WBRT is given, for patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.⁵⁴

Leptomeningeal Metastases

- ▶ Volume and dose depend on primary tumor histology and goals of care. For CSI in patients with metastatic solid tumor malignancies, techniques in maximizing bone marrow sparing should be considered (protons when available, or conformal photon-based techniques/IMRT).^{55,56}



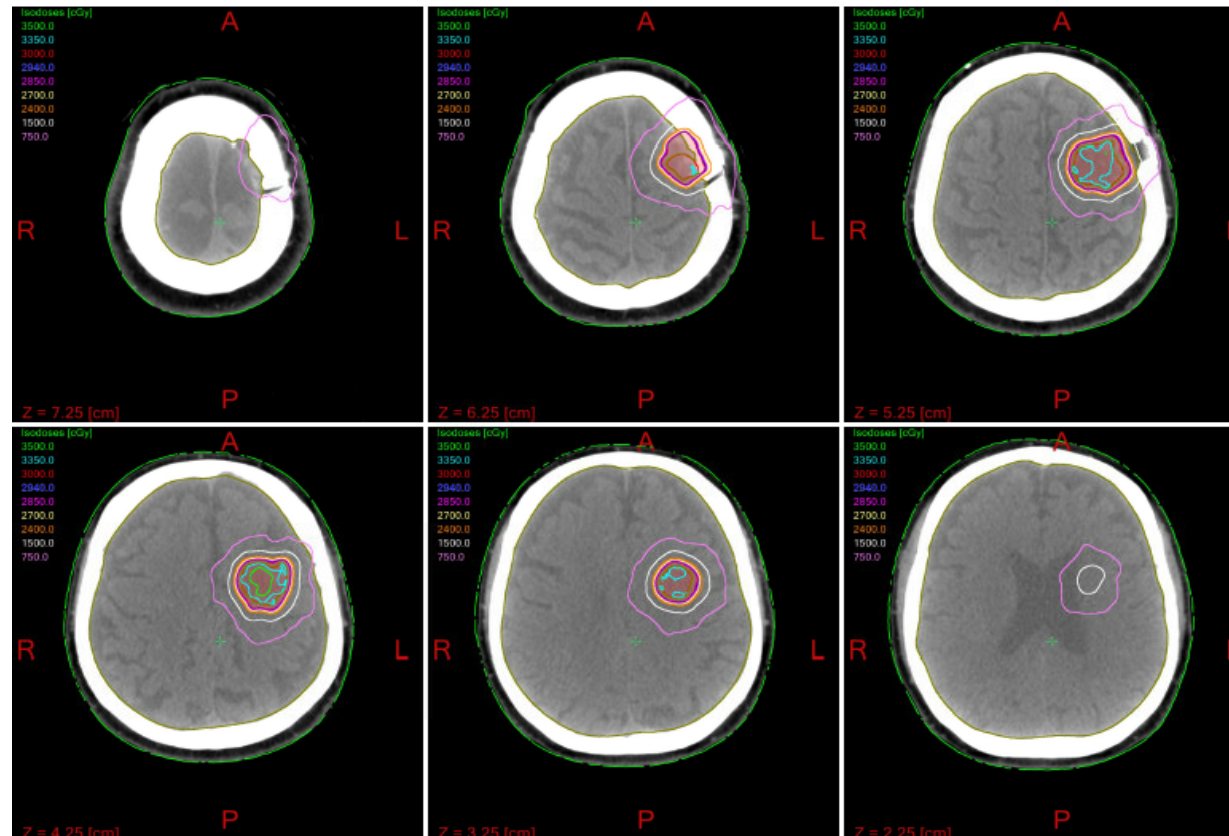
Radiation for Brain Metastases:

- **Stereotactic radiosurgery (SRS) achieves high local control rates for brain metastases, typically ranging from 82% to 90% for intact tumors and significantly reducing recurrence after surgical resection compared to observation alone.**
 - **Intact Tumors:** 1-year local control rates generally fall between 82% and 90% for small- to medium-sized lesions (typically ≤ 3 cm).
 - **Post-Operative (Cavity) SRS:** Delivering SRS to the surgical bed after tumor removal cuts down local recurrence significantly; 1-year freedom from local recurrence ranges roughly from 78% to 88% depending on tumor size and histology
 - **Impact of Size:** Smaller lesions (≤ 2.5 cm) show much higher freedom from local recurrence (up to 91% at 1 year) compared to larger tumors (> 3 cm), which face higher local failure rates with standard single-fraction doses.



Radiation for Brain Metastases:

- **Back to patient 1:**
 - **30Gy in 5 fractions to the post op cavity plus a small margin**



Radiation for Brain Metastases:

- **Key takeaways:**

- **Personalized Care:** Treatment choice depends on the **number of metastases**, tumor size, primary cancer type, and the patient's overall health.
- **SRS is Preferred:** SRS is the standard of care for limited metastases to protect cognitive function.
- **Multidisciplinary Approach:** Successful outcomes rely on close collaboration between neurosurgeons, radiation oncologists, and medical oncologists.

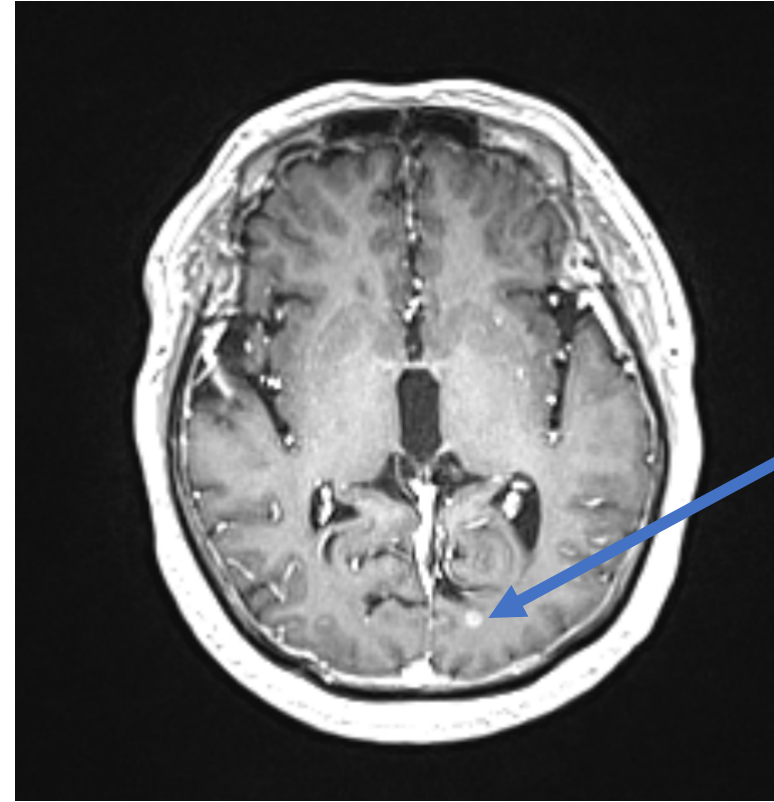
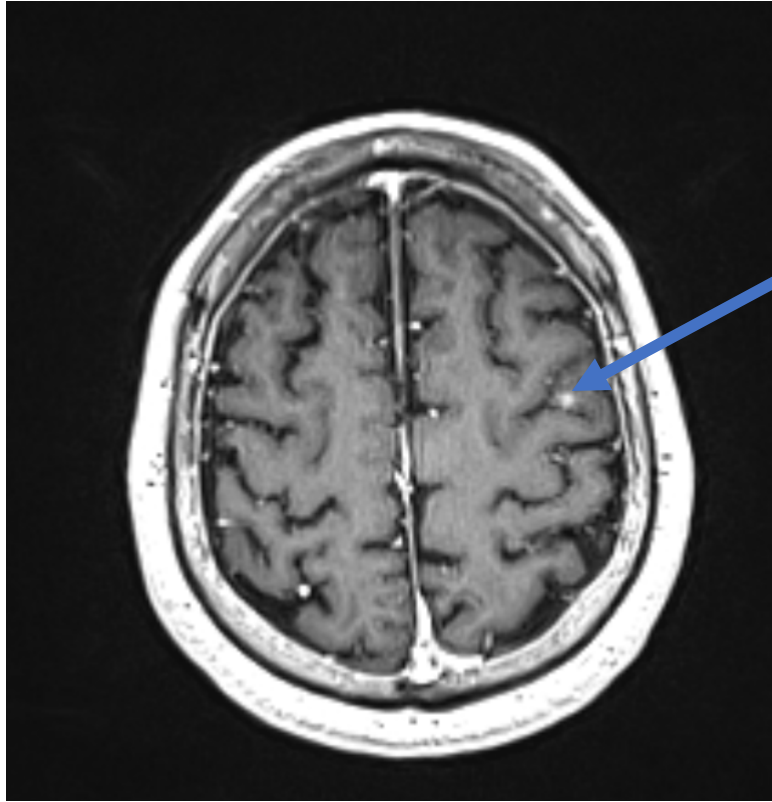


Patient 3

- 73 y.o. male, prior smoker with a 50 pack year smoking history (quit 6 years prior) presents with 3-4 months of a non-tender R submental and submandibular lymphadenopathy.
- Biopsy of R submental LN: Metastatic carcinoma consistent with metastatic lung adenocarcinoma.
- Denied drenching night sweats, cough, chest pain or shortness of breath. Denied headaches, changes in vision, N/V or any focal neural symptoms.
- ECOG 0.



Initial Workup



MRI Brain:

There are multiple enhancing lesions within the brain. Representative lesions are below:

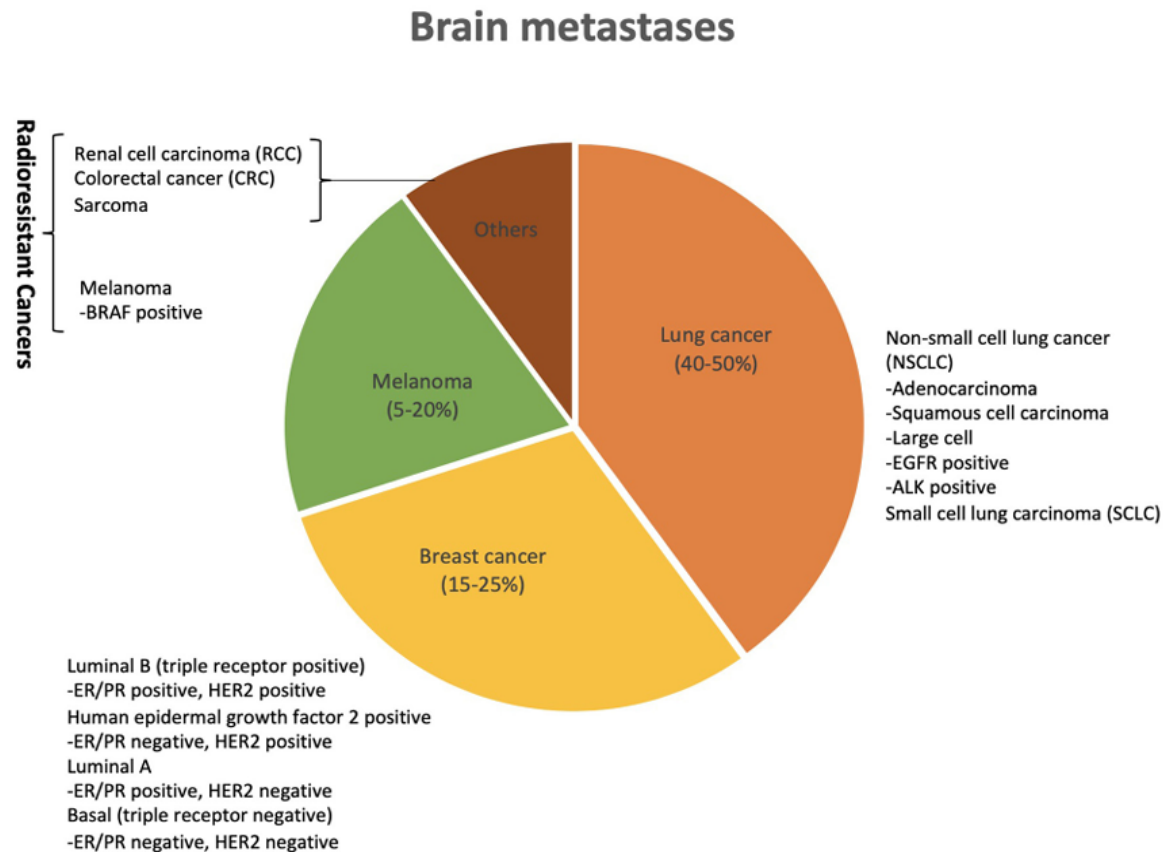
- There is an approximately 4 mm x 3 mm enhancing lesion within left frontal lobe.
- There is an approximately 5 mm x 5 mm enhancing lesion within the left occipital lobe.

There is no acute intracranial hemorrhage, midline shift, or hydrocephalus.

PET: 1. Hypermetabolic lymphadenopathy in the neck, chest, and abdomen including right cervical nodes, mediastinal, right hilar, and mesenteric nodes that are suspicious for nodal metastatic disease.



The Importance of this Topic



Metastatic Lung Cancer Trails:

- 11.4% included those with active, untreated BM
- 5.8% included LMD
- 7.8% evaluated CNS outcomes as an endpoint

Riano et al., *Clinical Lung Cancer*, 2025

Kahn et al., *Frontiers in Oncology*, 2020





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Central Nervous System Cancers

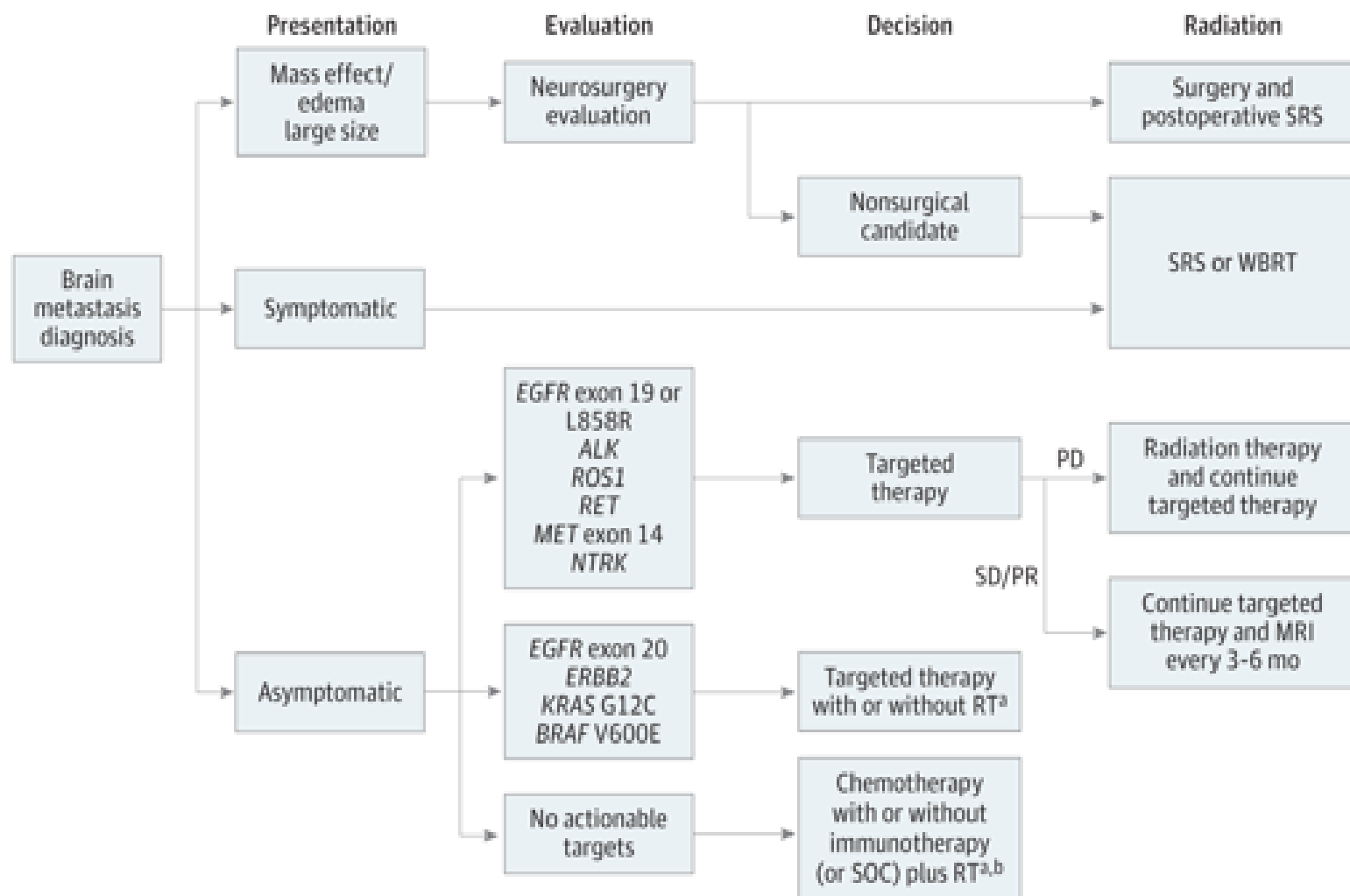
Version 3.2026 — August 17, 2026

[NCCN Guidelines for Patients®](#)

^f If an active agent exists (eg, cytotoxic, targeted, immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (eg, for patients with small asymptomatic brain metastases from melanoma or *ALK* gene fusion positive non-small cell lung cancer [NSCLC] or *EGFR*-mutated NSCLC); it is reasonable to hold on treating with radiation to see if systemic therapy can control the brain metastases. Consultation with a radiation oncologist and close MRI surveillance is strongly recommended. There are no data from prospective clinical trials comparing the two strategies to assess what the impact of delayed radiation would be in terms of survival or in delay of neurologic deficit development.



Potential Approach to Brain Mets from a Med Onc



Malhotra et al., *JAMA Oncology* 2025



A Proposed Schema

From: The role of upfront radiation therapy for brain metastases in the era of CNS-active systemic therapies: a narrative review of clinical trial design and lessons learned

Patient and systemic therapy (ST) characteristics	Treatment approach	Follow-up (FU)	Local therapy (LT) for new or progressive lesions
Asymptomatic and highly CNS active ST	Upfront ST only	Standard FU	
Asymptomatic and moderately CNS active ST	Upfront ST ± LT	Short 4-week FU	
Symptomatic or No/Low CNS active ST	Upfront ST + LT	Standard FU	

Proposed treatment and follow-up diagram for patient with newly diagnosed intact brain metastases according to symptom burden and intracranial activity of systemic therapy, defined as low (0–25%), intermediate (26–50%), or high (51–100%) intracranial objective response rate

Gal, Mehta, Kotecha, *J Neurooncol*, 2025



Specific Regimens to Consider

BRAIN METASTASES ^a : SYSTEMIC THERAPY ^b		
Tumor Agnostic	Breast Cancer ^c	Melanoma ^c
• <i>NTRK1/2/3</i> gene fusion ▶ Preferred ◊ Larotrectinib¹ ◊ Entrectinib² ◊ Repotrectinib³ • Other Recommended ◊ Temozolomide 5/28 Schedule • MSI-H/dMMR or TMB-H (≥10 mut/Mb) tumors for isolated brain metastases ▶ Preferred ◊ Pembrolizumab (category 2B)^{d,4,5,6}	• HER2 (<i>ERBB2</i>) positive ▶ Preferred ◊ Capecitabine/Tucatinib + Trastuzumab^e(category 1) if previously treated with ≥1 regimen⁷ ◊ Fam-trastuzumab deruxtecan-nxki if previously treated with ≥1 regimen^{8,9} ▶ Other Recommended ◊ Ado-trastuzumab emtansine (T-DM1)¹⁰ ◊ Ado-trastuzumab emtansine/Neratinib¹¹ ◊ Capecitabine/Lapatinib^{e,12,13} ◊ Capecitabine/Neratinib^{e,14,15} ◊ Pertuzumab + High-Dose Trastuzumab^{f,16} ◊ Neratinib/Paclitaxel (category 2B)¹⁷ • HER2 (<i>ERBB2</i>) non-specific ▶ Other Recommended ◊ Capecitabine^{e,18-22} ◊ Cisplatin (category 2B)^{23,24} ◊ Etoposide (category 2B)^{23,24} ◊ Cisplatin/Etoposide (category 2B)^{24,25} ◊ High-Dose Methotrexate/Leucovorin (category 2B)²⁶ • HER2 (<i>ERBB2</i>) low ▶ Useful in Certain Circumstances – Fam-trastuzumab deruxtecan-nxki (may also in patients with breast cancer that is HER2 (IHC) 1+ or 2+/in situ hybridization [ISH] negative)^{27,28}	• <i>BRAF</i> V600E positive ▶ Preferred ◊ Dabrafenib²⁹⁻³¹/Trametinib³² ◊ Cobimetinib^h/Vemurafenib^{33,34} (category 2B) • <i>BRAF</i> non-specific ▶ Preferred ◊ Ipilimumab + Nivolumab^{i,35-37} ▶ Other Recommended ◊ Ipilimumab³⁸ ◊ Nivolumab^{i,36} ◊ Pembrolizumab^{d,39}

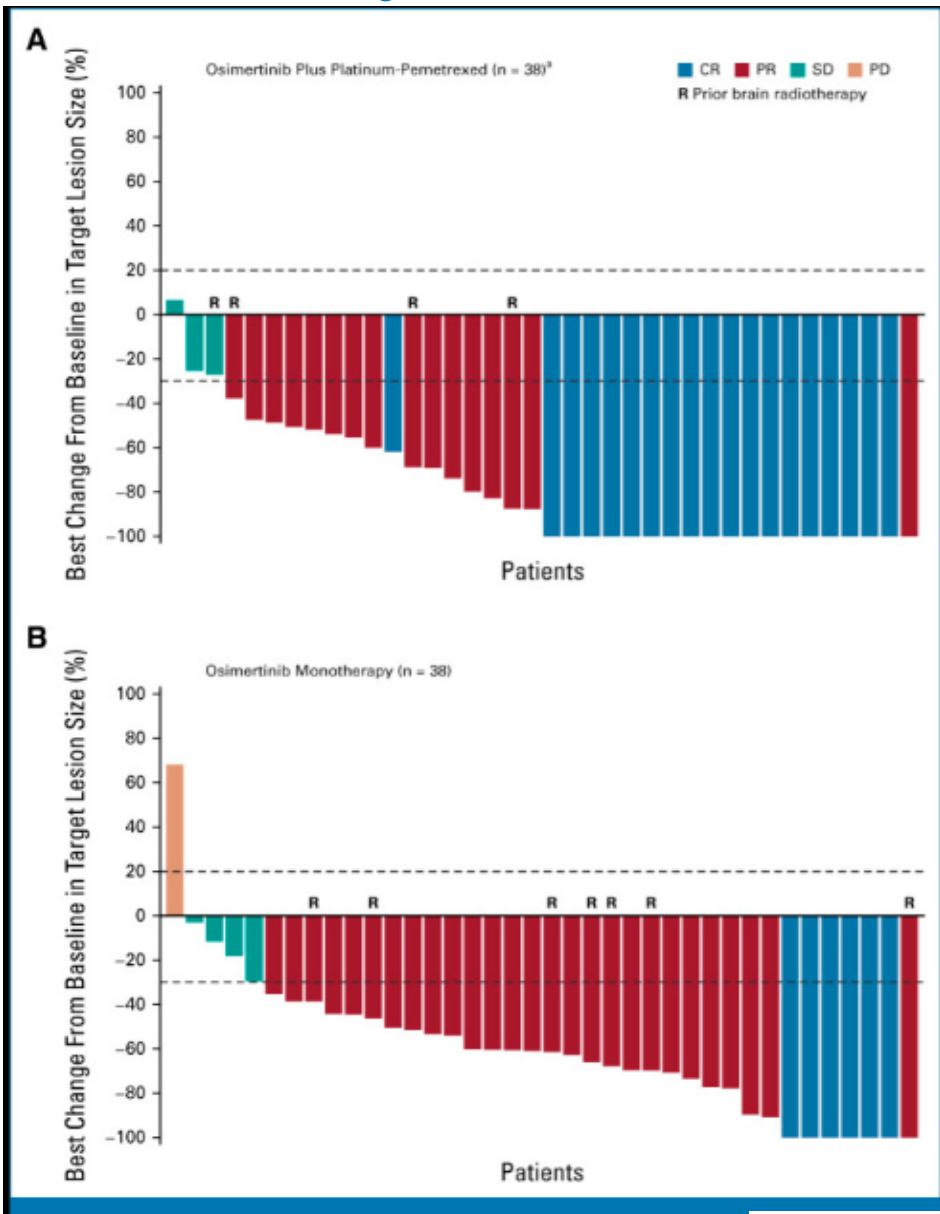
BRAIN METASTASES ^a : SYSTEMIC THERAPY ^b				
Non-Small Cell Lung Cancer (NSCLC) ^c		Small Cell Lung Cancer ^c	Lymphoma ^c	Renal Cell Carcinoma ^c
• <i>KRAS</i> G12C mutation ▶ Adagrasib^{40,41} ▶ Sotorasib (category 2B)^{42,43} • <i>EGFR</i>-sensitizing mutation positive ▶ Preferred ◊ Osimertinib⁴⁴⁻⁴⁷ ◊ Lazertinib + Amivantamab-vmjw^j (for exon 19 deletion or L858R)⁴⁸ ◊ Carboplatin/Pemetrexed + Amivantamab-vmjw^j (for exon 19 deletion or L858R)⁴⁹ ▶ Other Recommended ◊ Carboplatin/Osimertinib/Pemetrexed (category 1)⁵⁰ ◊ Cisplatin/Osimertinib/Pemetrexed (category 1)⁵⁰ ◊ Erlotinib⁵¹⁻⁵³ ◊ Afatinib (category 2B)⁵⁴ ◊ Gefitinib (category 2B)^{55,56} • <i>MET</i> exon 14 mutated ▶ Other Recommended ◊ Capmatinib⁵⁷ ◊ Tepotinib^{58,59}	• <i>RET</i> gene fusion positive ▶ Selpercatinib⁶⁰ • <i>ALK</i> gene fusion positive ▶ Preferred ◊ Brigatinib^{61,62} ◊ Lorlatinib⁶³ ◊ Alectinib^{64,65} ◊ Ceritinib⁶⁶ • <i>ALK</i> gene fusion positive or <i>ROS1</i> gene fusion positive ▶ Crizotinib (category 2B)⁶⁷ • <i>ROS1</i> gene fusion positive ▶ Repotrectinib⁶⁸ ▶ Taletrectinib^{69,70} • PD-L1 positive ▶ Other Recommended ◊ Pembrolizumab^{d,39,71} (tumor proportion score [TPS] ≥1%) ◊ Nivolumab^{i,72-74} (TPS ≥1%)	• Tarlatamab-dlle⁷⁵ • Topotecan (category 2B)	• High-Dose Methotrexate/Leucovorin⁷⁶ • BTK inhibitor (eg, Ibrutinib)⁷⁷	• Cabozantinib⁷⁸ • Belzutifan (category 2B)⁷⁹ (for VHL-associated renal cell carcinoma [RCC])

Case Presentation Continued

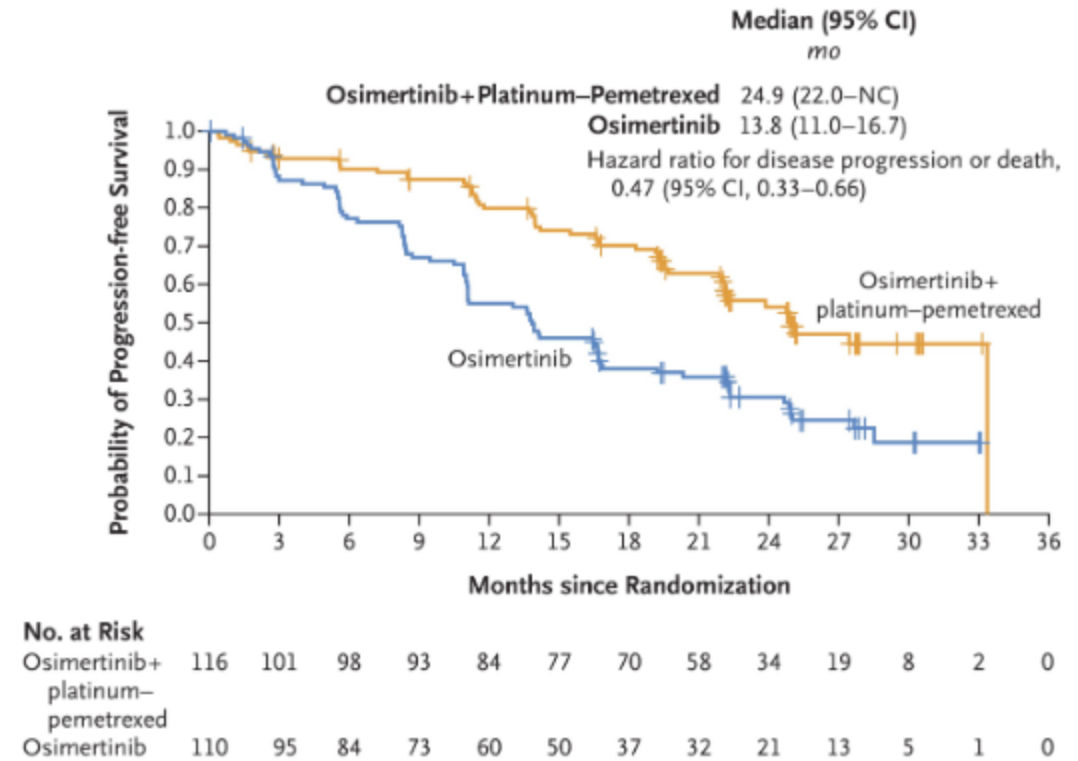
- Referral to Radiation Oncology who saw patient and discussed SRS but as lesions were small and asymptomatic could wait for moleculars, as some targetable mutations of high intracranial penetration.
- Guardant: EGFR L858R, TP53 C176Y , TP53 K164fs



Systemic Therapy: A Viable Alternative



C Progression-free Survival among Patients with CNS Metastases at Baseline



Planchard et al., *New England Journal of Medicine*, 2023

Jänne et al., *JCO*, 2024



Close Surveillance is Required

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NCCN Guidelines Index

Table of Contents

Discussion

NCCN Guidelines Version 3.2026

Limited Brain Metastases

FOLLOW-UP ^a	RECURRENCE	TREATMENT	
Brain MRI ^a every 2–3 ⁿ mo for 1–2 y then every 4–6 mo indefinitely ^p	Recurrent disease after radiation; local site ^o	Surgery ^d followed by SRS or RT to the surgical bed ⁱ or Laser interstitial thermal therapy (LITT) ^f or SRS ^{i,q} or HA-WBRT ^{i,m} for large volumes + memantine ^m or WBRT ⁱ for large volumes without HA ± memantine or Consider systemic therapy ^{g,s}	
	Recurrent disease after radiation; distant brain ± local recurrence	Limited brain metastases ^c	Surgery followed by SRS to the surgical bed ⁱ or SRS ^{i,q} or HA-WBRT ^{i,m} for large volumes if not previously administered + memantine or WBRT ⁱ for large volumes if not previously administered without HA ± memantine ^m or Consider systemic therapy ^{g,s}
		Extensive brain metastases	HA-WBRT ^{i,m} if not previously administered + memantine or WBRT ⁱ if not previously administered without HA ± memantine or Consider systemic therapy ^{g,s}

Brain MRI^a every 2–3ⁿ mo for 1–2 y then every 4–6 mo indefinitely^p

→

Brain MRI^a every 2–3ⁿ mo for 1–2 y then every 4–6 mo indefinitely^p

Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on LTD-3A

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NCCN Guidelines Index

Table of Contents

Discussion

NCCN Guidelines Version 3.2026

Extensive Brain Metastases

FOLLOW-UP ^a	RECURRENCE	TREATMENT
Brain MRI every 2–3 mo for 1–2 y, then every 4–6 mo indefinitely ^k	Systemic disease progression, with limited systemic treatment options	Palliative/best supportive care
	Stable systemic disease or reasonable systemic treatment options	Surgery or SRS ^e or HA-WBRT ^{e,i} + memantine or WBRT ^e without HA ± memantine or Systemic therapy ^j

Brain MRI every 2–3 mo for 1–2 y, then every 4–6 mo indefinitely^k

→

Recurrent disease^l

→

Brain MRI^a every 2–3 mo for 1–2 y, then every 4–6 mo indefinitely^k



Outcome

- MRI Brain 6 weeks after starting FLAURA 2 regimen: "Resolution of previously noted intracranial enhancing lesions. No new intracranial metastatic disease."
- Pt is currently on cycle 25 and maintains a CR

Thank You

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