2023 Oncology Fellows Program:
New Horizons in Quality Cancer Care™

Management of Central Nervous System Metastases

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Learning Objectives

- Describe advances in diagnosis and treatment of brain metastases.
- Understand the evidence supporting stereotactic radiosurgery and whole brain radiation therapy for treatment of brain metastases, as well as potential effects on cognitive function and quality of life.
- Identify emerging systemic therapy options for patients with brain metastases, including targeted therapies.

Epidemiology - General

- Brain metastases are most common tumor of central nervous system
  - 7-14 persons per 100,000 population → 50,000 cases a year US
- Brain metastases may be more frequent in some tumor types
  - Taxanes and other drugs may allow isolated CNS recurrences
  - Breast, ovary, lung, uterine have increasing isolated brain metastases
- Lung cancer accounts for the highest number of brain metastases (25% of patients will develop)
- The incidence is felt to be increasing with new and more effective systemic cancer treatment

Maher, Cancer Res 2009

Epidemiology – Breast Cancer Brain Metastases

- Second leading systemic cancer with CNS metastases – 10-16%
- Characteristics of CNS disease
  - Site is much more likely to be parenchymal than leptomeningeal
  - Neurological symptoms typically reason for discovery
  - More likely to be in setting of progressive systemic disease*
- Risk is not equal among the breast cancer subtypes
  - HER-2 positive
  - Triple negative (ER neg, PR neg, and HER-2 neg)
- Mechanism and outcomes are not the same among those with the highest risk
  - HER-2 positive
  - Triple negative (ER neg, PR neg, and HER-2 neg)

De Ieso et al., Breast 2015

Presenting Signs and Symptoms

Generalized

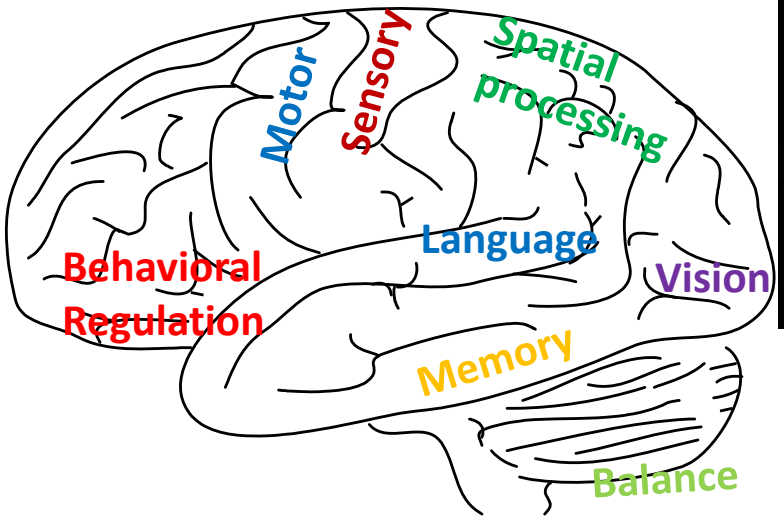
- Headache
- Neurocognitive changes
- Mood or personality changes
- Seizures

Focal

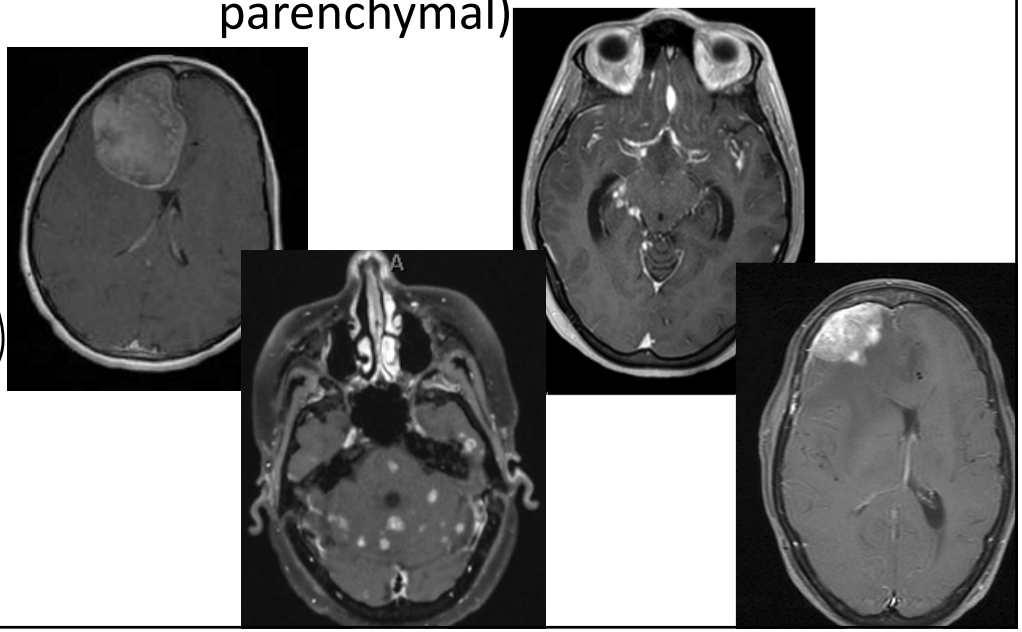
- Slurred speech/aphasia
- Visual changes (field)
- Hemiparesis or sensory loss
- Ataxia

Cancer in the CNS – Location Matters

- Functional Location
- the CNS functional location (neurological impact)

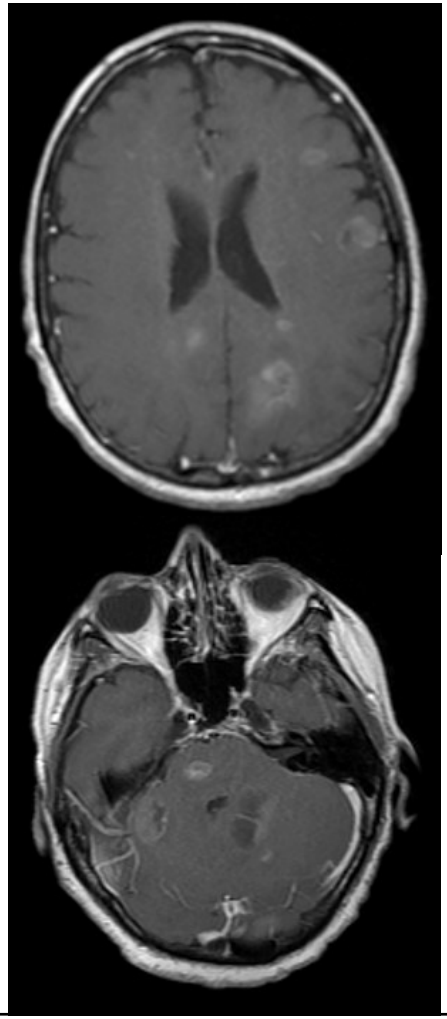


- Physical Location
- the physical location (dural, LM, parenchymal)



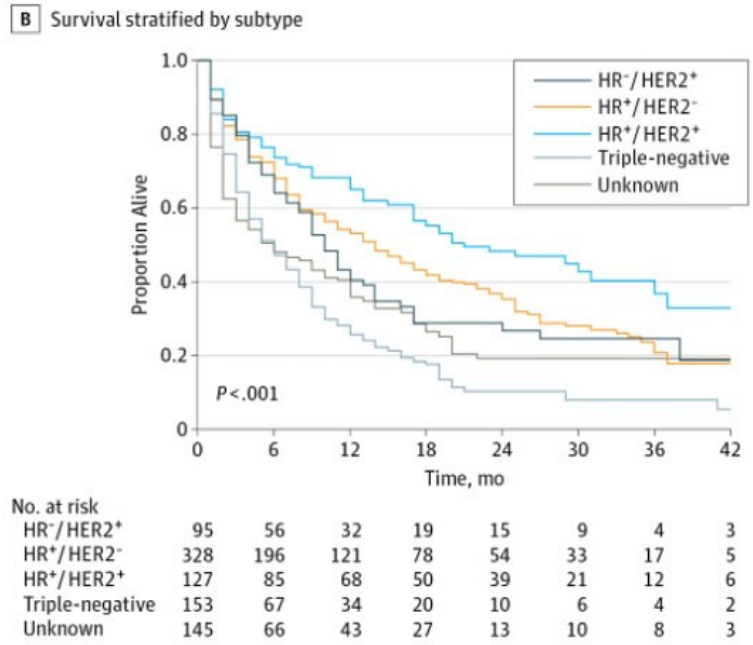
Initial Evaluation

- MR brain with and without contrast
- CT with and without contrast if MR contraindicated
- Consider need for systemic staging update
- Neurosurgical consultation
  - Management of mass effect
  - Need for diagnostic tissue
  - Management of disease
- Role of corticosteroids



Brain Metastasis: Covariates Affecting Survival

- Age
- Performance status*
- Controlled primary disease
- Isolated brain disease
- Solitary versus multiple metastases
- RTOG RPA class
  - GPA (Graded Prognosis Assessment)
    - Sperduto et al., IJROBP 2008; 70
    - Sperduto et al., IJROBP 2020; 107
- Breast cancer subtype*

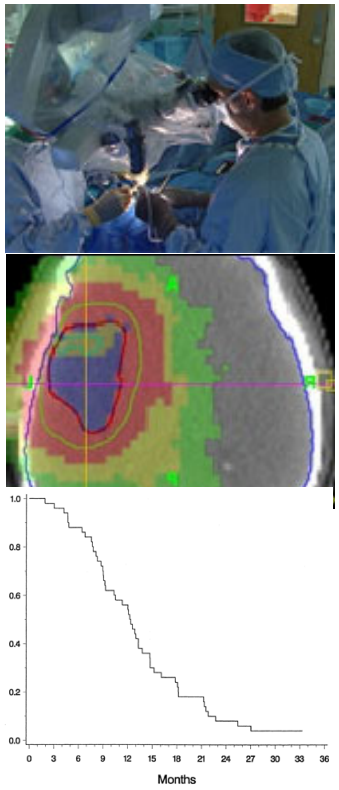


*-largest impact on OS

Martin et al, JAMA Oncology 2017

Primary Treatment Modalities

- Surgery
- Radiation therapy
  - Stereotactic radiosurgery (SRS)
  - Whole brain radiation therapy (WBRT)
- Systemic therapy

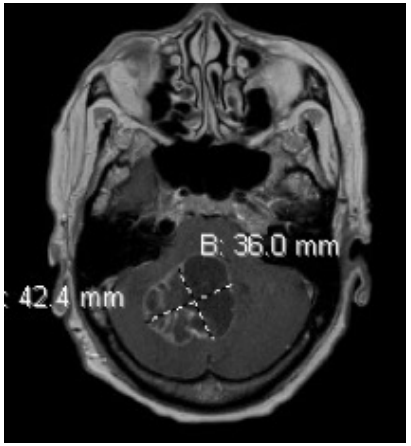


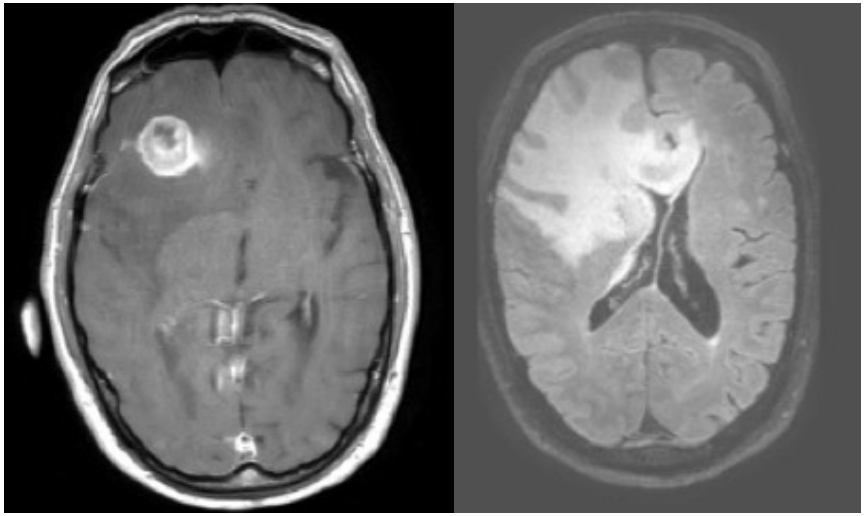
Neurosurgery Applications

- Management of elevated intracranial pressure
  - All evidence-based guidelines assert the role of local therapies in management of brain metastases
- Reduction in symptom burden and improvement in neurological function
- Tissue for NGS as up to 50% BMs have treatable molecular alterations not present in the primary tumor (Brastianos et al., *Cancer Discovery* 2015)
- Not all intracranial lesions are metastasis in patients with metastatic cancer (Patchell et al., *NEJM* 1990)

Proescholdt et al., *Cancers* 2021

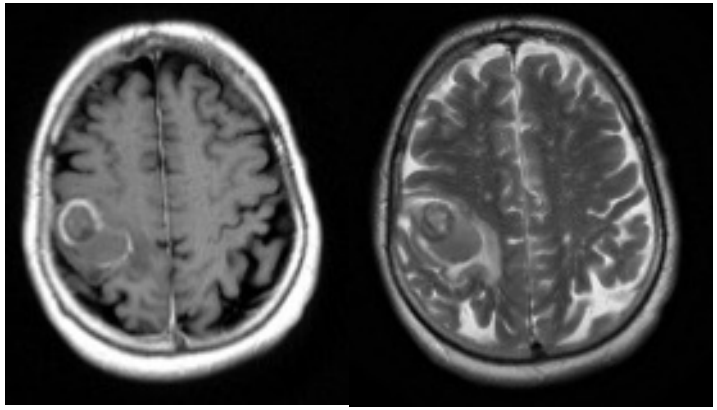
Posterior fossa location





Mass effect

Motor dysfunction



Radiation Therapy Applications

- Upfront primary line of therapy for local control
  - All evidence-based guidelines assert the role of local therapies in management of brain metastases
- As an adjunct to surgery following resection of the tumor, delivered to the surgical resection cavity
- Single fraction treatment to hypo-fractionated 3-5 fractions based on the treatment volume
- As a boost treatment to maximize local control following WBRT

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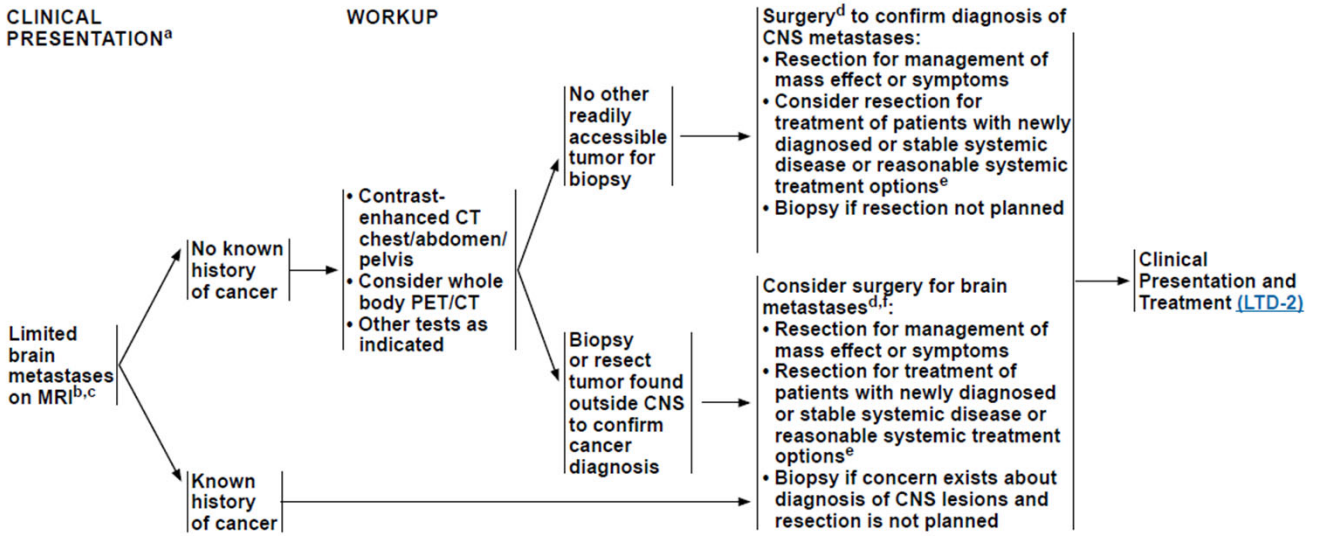
Limited Brain Metastases



[a] Principles of Brain and Spine Tumor Imaging (BRAIN-A).
[b] Consider a multidisciplinary review in treatment planning, especially once pathology is available. See Principles of Brain and Spine Tumor Management (BRAIN-D).
[c] "Limited" brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. The definition of "limited" brain metastases in terms of number of metastases or total intracranial disease volume is evolving and may depend on the specific clinical situation (Yamamoto M, et al. Lancet Oncol 2014;15:387-395).
[d] Principles of Brain Tumor Surgery (BRAIN-B).
[e] For secondary CNS lymphoma, treatment may include systemic treatment, WBRT or focal RT, or a combination.
[f] The decision to resect a tumor may depend on the need to establish histologic diagnosis, the size of the lesion, its location, and institutional expertise. For example, smaller (<2 cm), deep, asymptomatic lesions may be considered for treatment with SRS versus larger (>2 cm), symptomatic lesions that may be more appropriate for surgery (Ewend MG, et al. J Natl Compr Cancer Netw 2008;6:505-513).

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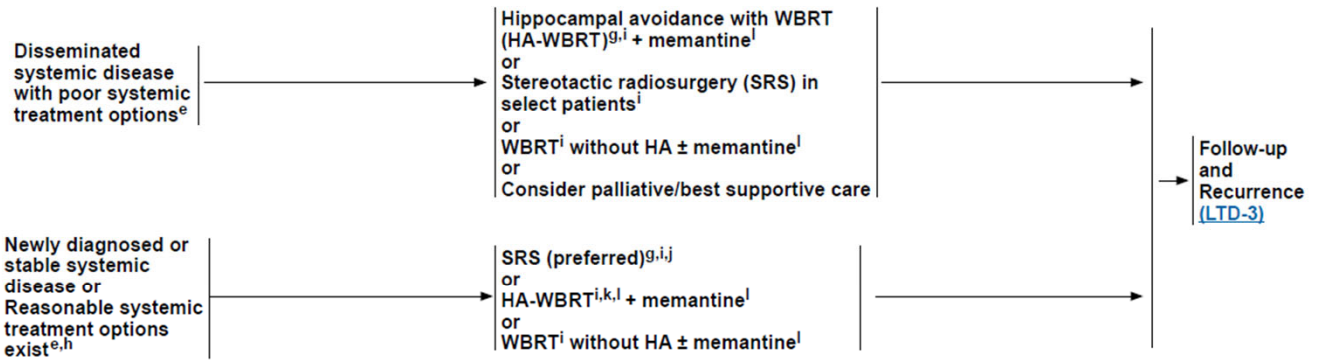
Limited Brain Metastases



[e] For secondary CNS lymphoma, treatment may include systemic treatment, WBRT or focal RT, or a combination.

[g] 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* rearrangement-positive non-small cell lung cancer [NSCLC] or epidermal growth factor receptor [*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.

[h] Brain Metastases Systemic Therapy (BRAIN METS-A).

[i] Principles of Radiation Therapy for Brain and Spinal Cord (BRAIN-C).

[j] SRS is preferred when safe, especially for low tumor volume, to both the resection cavity and any other non-resected brain metastases. WBRT is generally not recommended but may be appropriate in some rare clinical circumstances.

[k] For brain metastases not managed with resection, SRS + WBRT is generally not recommended, as the addition of WBRT to SRS does not improve survival and can be associated with greater cognitive decline and poorer quality of life (Brown PD, et al. JAMA 2016;316:401-409). However, the combination of SRS and WBRT may be appropriate in carefully selected clinical circumstances (eg, WBRT is already being offered for extensive brain metastases and an SRS boost is considered for a large lesion or radioresistant histology for the goal of improving local control) (Andrews DW, et al. Lancet 2004;363.9422:1665-1672).

[l] Brain metastases not within 5 mm of the hippocampi; life expectancy of at least 4 months. In patients without brain metastases within 5 mm of the hippocampi, HA-WBRT + memantine was superior to WBRT + memantine in terms of cognitive preservation and patient-reported quality of life (Brown PD, et al. J Clin Oncol 2020:38:1019-1029 and Brown PD, et al. Neuro Oncol 2013:15:1429-1437).

Brain Metastasis and Neurocognition

- Majority of patients with brain metastasis have neurologic and neurocognitive impairment
- Neurocognitive > physical
  - prevents functional independence
- Concern radiation therapy may lead to neurocognitive impairment

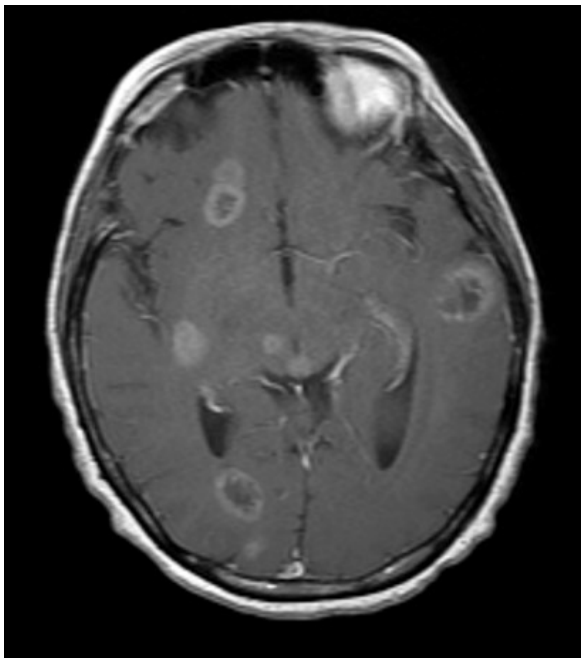


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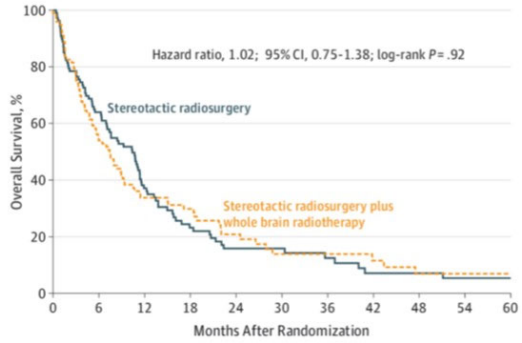
Figure 3. Kaplan-Meier Estimates of Overall Survival According to Treatment Group



No. at risk

Stereotactic radiosurgery	111	64	35	19	13	10	7	4	4	2	2
Stereotactic radiosurgery plus whole brain radiotherapy	102	50	28	22	13	8	8	5	3	1	1

- No difference in overall survival but worse cognition with addition of WBRT to SRS
- Other considerations: hippocampal avoidance and donepezil or memantine

Table 2. Patients Who Experienced Cognitive Deterioration by 3 Months and Difference Between Groups

	No. (%) of Participants			
	SRS Alone (n = 63)	SRS Plus WBRT (n = 48)	Mean Difference, % (95% CI)	*P* Value[a]
Change from baseline[b]				
HVLT-R				
Immediate recall				
Deterioration	5 (8.2)	14 (30.4)	22.2 (5.4 to 39.1)	.004
No deterioration	56 (91.8)	32 (69.6)		
Delayed recall				
Deterioration	12 (19.7)	24 (51.1)	31.4 (12.1 to 50.7)	<.001
No deterioration	49 (80.3)	23 (48.9)		
Recognition				
Deterioration	14 (22.6)	19 (40.4)	17.8 (−1.5 to 37.2)	.06
No deterioration	48 (77.4)	28 (59.6)		
TMT-A time to complete				
Deterioration	10 (16.7)	14 (30.4)	13.8 (−4.4 to 32.0)	.11
No deterioration	50 (83.3)	32 (69.6)		
TMT-B time to complete				
Deterioration	11 (19.0)	16 (37.2)	18.2 (−1.4 to 37.9)	.07
No deterioration	47 (81.0)	27 (62.8)		
COWAT total				
Deterioration	1 (1.9)	8 (18.6)	16.7 (2.4 to 31.0)	.01
No deterioration	52 (98.1)	35 (81.4)		
GPS total seconds				
Deterioration	17 (29.3)	21 (47.7)	18.4 (−2.4 to 39.3)	.07
No deterioration	41 (70.7)	23 (52.3)		
Outcome for cognitive progression at 3 mo				
Stable	23 (36.5)	4 (8.3)	−28.2 (−44.2 to −12.2)	<.001
Progression	40 (63.5)	44 (91.7)		

Brown et al *JAMA*. 2016;316(4):401-409
See also Chang et al, Lancet Oncology. 2009;20(11):1037-1044
Brown et al, Lancet Oncology. 2017;18(8):1049-1060

Clinical Practice Implications

- Local therapies are the mainstay of cancer brain metastases
- The addition of WBRT to SRS may not significantly improve OS but leads to a decline in cognition
- The definition of ”limited” brain metastasis is evolving and driven more by intracranial volume of disease than absolute number
- Factors influencing improved outcomes with the addition of WBRT to SRS
  - Hippocampal avoidance strategies
  - Medication considerations

Systemic Therapy Considerations in Brain Metastases

- Solitary lesions benefit significantly from local therapy
  - BM 35% solitary lesion, 25% 2-3 lesions (Sperduto et al., IJROBP 2020; 107)
- Local therapy remains mainstay of treatment for multiple lesions with lesion volume more critical than absolute number
- Factors to consider when using systemic therapy for BM:
  - Status of systemic disease
  - Type of CNS presentation: parenchymal, dural, or leptomeningeal
  - Agent access to the CNS
  - If breast cancer, consider the subtype

2012 NCCN CNS Tumor page for systemic therapy

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Central Nervous System Cancers

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CNS Table of Contents
Discussion

PRINCIPLES OF BRAIN AND SPINAL CORD TUMOR SYSTEMIC THERAPY

Limited (1-3) Metastatic or Multiple (> 3) Metastatic Lesions

- Recurrent Disease‡
  - Treatment as per the regimens of the primary tumor
  - Carmustine wafer[50]
- Temozolomide 5/28 schedule
- Organ specific therapy
  - High dose methotrexate[51,52] (breast[51] and lymphoma)
  - Capecitabine ± lapatinib,[53,54] cisplatin,[55,56] etoposide[55,56] (breast)[57-61]
  - Topotecan (small cell lung)

Leptomeningeal Metastases

- Treatment
  - Organ specific systemic chemotherapy; emphasizing drugs with good CNS penetration
  - Intra-CSF chemotherapy[62] (liposomal cytarabine,[63,64] methotrexate,[9] cytarabine, thiotepa, rituximab,[64] topotecan,[65] etoposide,[66] interferon alfa[67])
  - High-dose methotrexate for lymphomatous meningitis[52]

Metastatic Spine Tumors

- Use regimen for disease specific site

‡Use agents active against primary tumor.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

References on next page

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Brain Metastases

BRAIN METASTASES[a]: SYSTEMATIC THERAPY

- Tumor Agnostic[b]
  - *NTRK* gene fusion tumors
    - ◊ Preferred Regimens
      - – Larotrectinib[1]
      - – Entrectinib[2]
    - ◊ Other Recommended Regimens
      - – TMZ 5/28 schedule
- Breast Cancer[c]
  - HER2 positive
    - ◊ Preferred Regimens
      - – Tucatinib + trastuzumab[d] + capecitabine (category 1) (if previously treated with 1 or more anti-HER2–based regimens)[3]
    - ◊ Other Recommended Regimens
      - – Ado-trastuzumab emtansine (T-DM1)[4]
      - – Capecitabine + lapatinib[5,6]
      - – Capecitabine + neratinib[7,8]
      - – Fam-trastuzumab deruxtecan-nxki[9,10]
      - – Pertuzumab and high-dose trastuzumab[d,11]
      - – Paclitaxel + neratinib (category 2B)[12]
  - HER2 non-specific
    - ◊ Other Recommended Regimens
      - – Capecitabine[13-17]
      - – Cisplatin (category 2B)[18,19]
      - – Etoposide (category 2B)[18,19]
      - – Cisplatin + etoposide (category 2B)[19,20]
      - – High-dose methotrexate (category 2B)[e,21]
- Melanoma[c]
  - *BRAF* V600E positive
    - ◊ Preferred Regimens
      - – Dabrafenib[22-24]/trametinib[25]
      - – Vemurafenib[26,27]/cobimetinib[f] (category 2B)
- Melanoma[c]
  - *BRAF* non-specific
    - ◊ Preferred Regimens
      - – Ipilimumab + nivolumab[28-30]
    - ◊ Other Recommended Regimens
      - – Ipilimumab[31]
      - – Nivolumab[29]
      - – Pembrolizumab[32]
- Non-Small Cell Lung Cancer[c]
  - *KRAS* G12C mutation
    - ◊ Adagrasib[33,34]
  - EGFR-sensitizing mutation positive
    - ◊ Preferred Regimens
      - – Osimertinib[35-37]
    - ◊ Other Recommended Regimens
      - – Pulsatile erlotinib[38-40]
      - – Afatinib (category 2B)[41]
      - – Gefitinib (category 2B)[42,43]
  - *MET* exon 14 mutated
    - ◊ Other Recommended Regimens
      - – Capmatinib[44]
      - – Tepotinib[45,46]
  - *RET* fusion positive
    - ◊ Selpercatinib[47]
  - *ALK* rearrangement positive
    - ◊ Preferred Regimens
      - – Brigatinib[48,49]
      - – Lorlatinib[50]
      - – Alectinib[51,52]
      - – Ceritinib[53]
  - *ALK* rearrangement positive or *ROS1* positive
    - ◊ Crizotinib (category 2B)[54]
  - PD-L1 positive
    - ◊ Other Recommended Regimens
      - – Pembrolizumab[32,55] (Tumor Proportion Score [TPS] ≥1%)
      - – Nivolumab[56-58] (TPS ≥1%)
- Small Cell Lung Cancer[c]
  - ◊ Topotecan (category 2B)
- Lymphoma[c]
  - ◊ High-dose methotrexate[59]
  - ◊ BTK inhibitor (eg, ibrutinib)[60]
- Renal Cell Carcinoma[c]
  - Cabozantinib[61]

HER2+ BCBM

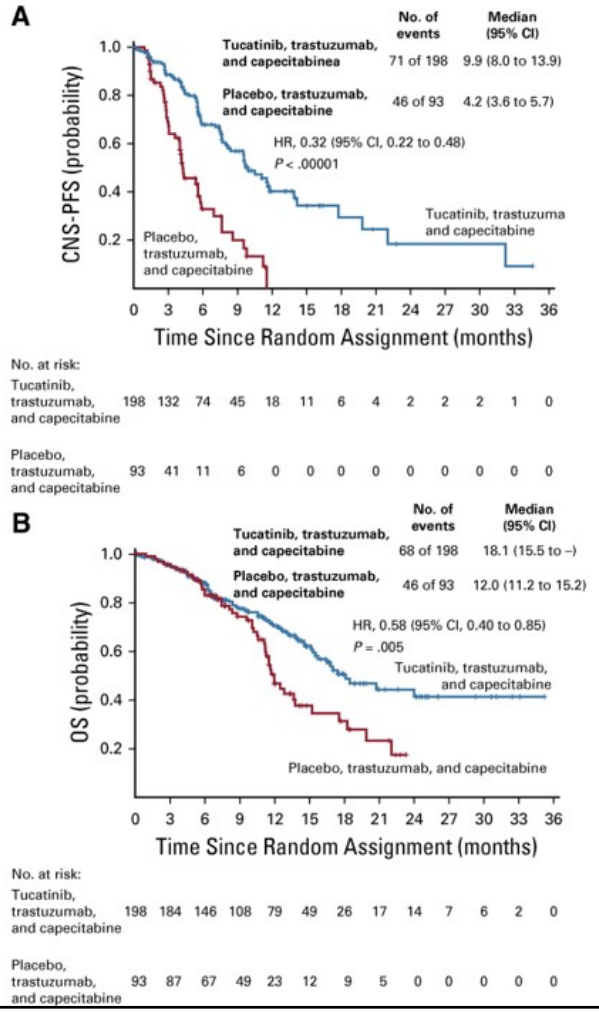
- Trastuzumab improves OS in HER2+ breast cancer (Slamon et al, NEJM 2001)
- CNS as a ”sanctuary” site
  - High percent patients with HER2+ mBC develop brain metastases
- HER2+ patients continuing anti-HER2 therapy after BM do better
  - OS 15.7 months vs 4.4 months (Brufsky et al., Clin Cancer Res 2011; Pestalozzi et al., Lancet Oncology 2013)
- HER2+ patients with BM cause of death more likely neurological progression over systemic progression (69% and 29.8%) (De Ieso et al., Breast 2015)
- Role of screening for BM in HER2+

Targeted Agents in HER2+ BCBM

- Lapatinib
  - Tyrosine kinase inhibitor to EGFR (ErbB1) and HER2 (ErbB2)
  - Crosses BBB
  - BCBM
    - Single agent low response rates
    - Intracranial response rate improves with addition of capecitabine
    - RR 66%, Time to IC prog – 5.5 mos
      - Bachelot et al., Lancet Oncol 2013
- Neratinib
  - Tyrosine kinase inhibitor to EGFR (ErbB1), HER2 (ErbB2) and HER3 (ErbB3)
  - BCBM
    - Single agent low response rates
    - Combination with capecitabine and paclitaxel in treatment or reducing incidence of BCBM
      - Saura et al, JCO 2020
      - Awada et al, JAMA Oncol 2016

HER2CLIMB

- HER2+ metastatic breast cancer with brain mets
- Tucatinib in combination with trastuzumab and capecitabine
- Results:
  - Reduce brain progression (CNS-PFS) by 68%
  - Reduced risk of death (OS) by 42%
  - Doubled IC ORR (47% to 20%)



Murthy et al., NEJM 2020
Lin et al., JCO 2021

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Central Nervous System Cancers

PRINCIPLES OF BRAIN AND SPINE TUMOR MANAGEMENT

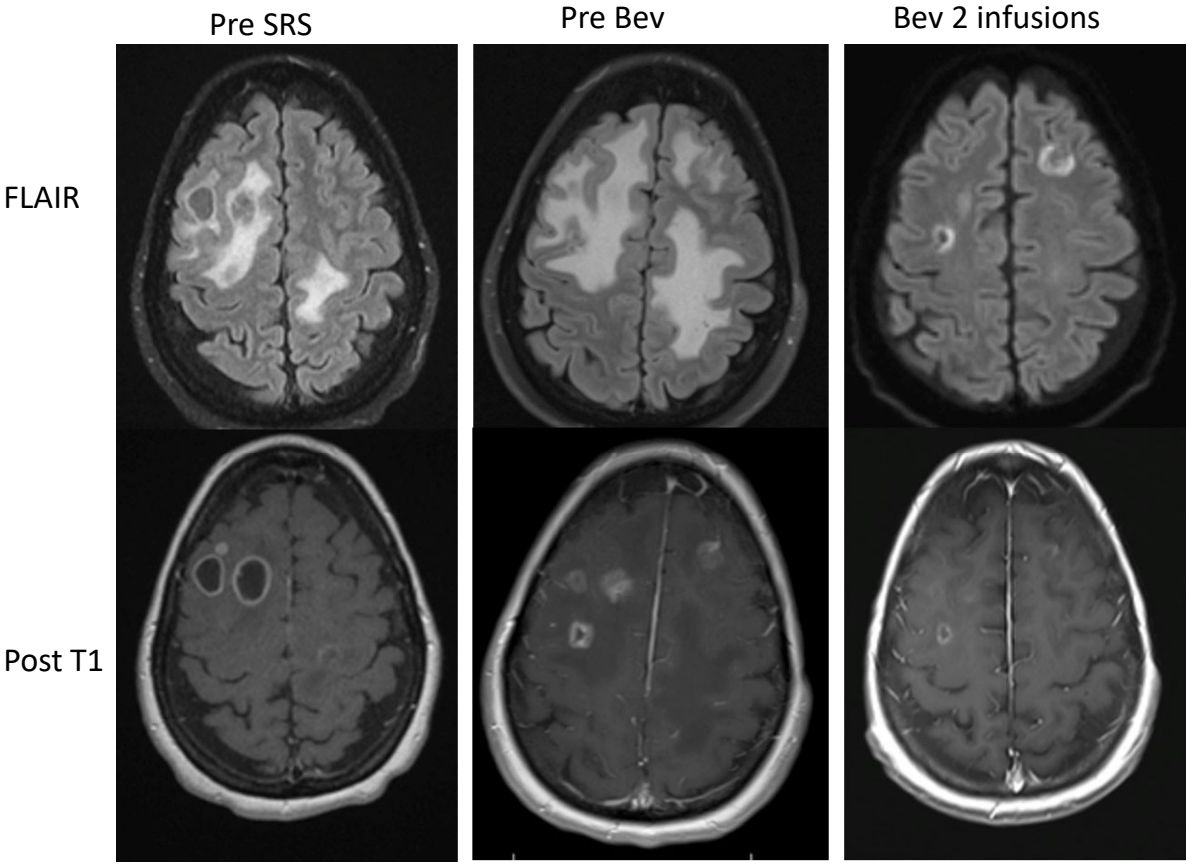
Multidisciplinary Care (continued)

- Practitioners should become familiar with palliative and hospice care resources that are available in their community in order to help educate patients and families that involvement of these services does not indicate a state of hopelessness, no further treatment, or abandonment. Palliative and pain management care should be integrated into management of neuro-oncology patients early in the course of their treatment[1] (NCCN Guidelines for Palliative Care).

Medical Management

1. Corticosteroids
   - Steroid therapy should be carefully monitored. If a patient is asymptomatic, steroids may be unnecessary. In general, the lowest dose of steroids should be used for the shortest time possible.[b] Downward titration of the dose should be attempted whenever possible. Twice-daily (BID) or once daily dosing is recommended for dexamethasone. Patients with extensive mass effect should receive steroids for at least 24 hours before RT. Patients with a high risk of gastrointestinal (GI) side effects (ie, perioperative patients, prior history of ulcers/GI bleed, receiving nonsteroidal anti-inflammatory drugs [NSAIDs] or anticoagulation) should receive H2 blockers or proton pump inhibitors. Care should be taken to watch for development of steroid side effects.[c]
   - Consider prophylactic treatment of pneumocystis jiroveci pneumonia (PJP) for patients undergoing long-term steroid therapy (NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections).
2. Mass Effect, Brain Edema, Radiation Necrosis
   - Careful questioning for subtle symptoms should be undertaken if edema is extensive on imaging.
   - Consider short-course bevacizumab for management of symptoms driven by RT necrosis,[2,3] poorly controlled vasogenic edema, or mass effect in patients with brain metastases and primary brain tumors, particularly those with deep-seated unresectable tumors, as it may allow overall quality-of-life improvements by reducing steroid dose and improving functional status.[4]
   - LITT is a minimally invasive technique using photothermal technology and can be considered on a case-by-case basis for treatment of radiation necrosis in patients with a history of RT for primary brain tumor or metastatic disease.[5,6] Consultation with adept neurosurgeons trained in LITT should be done when the procedure is considered.
3. Seizures
   - Seizures are frequent in patients with primary or metastatic brain tumors. Despite this, studies have shown that the use of older, "traditional" anti-seizure medications, including phenytoin, phenobarbital, and valproic acid as prophylaxis against seizures in patients who have never had a seizure or who are undergoing neurosurgical procedures, is ineffective and is not recommended. Newer agents (ie, levetiracetam, topiramate, lamotrigine, pregabalin) have not yet been systematically studied.
   - Seizure prophylaxis is not recommended as routine in asymptomatic patients but is reasonable to consider perioperatively.
   - Many anti-seizure medications have significant effects on the cytochrome P450 system, and may have effects on the metabolism of numerous chemotherapeutic agents such as irinotecan, gefitinib, erlotinib, and temsirolimus among others. When possible, such enzyme-inducing antiepileptic drugs (EIAEDs) should be avoided (ie, phenytoin, phenobarbital, carbamazepine), and non-EIAEDs should be used instead (ie, levetiracetam, topiramate, valproic acid, lacosamide). Patients should be closely monitored for any adverse effects of the anti-seizure medications or chemotherapeutic agents.

References (BRAIN-D 5 of 5)



Bevacizumab for acute neurologic deterioration

- Consider in setting of significant vasogenic edema
- Improves neurological function
- Reduces steroid requirements
- Short course and low dose
- Can also be considered in inpatient setting

Kaley et al., CNS Oncol 2013

Key Points

- BM develop in 30% of patients with solid cancer
  - Breast cancer is second leading source of brain metastatic disease
- Do not overlook the role of neurosurgical intervention
- SRS is the primary treatment for limited and multiple BM
- WBRT improves disease control in the brain after SRS but comes with a neurocognitive cost
- Systemic therapy options are rapidly expanding for BM
  - Caution and multidisciplinary recommendations when holding SRS for systemic option
- Consider short-term bevacizumab for treatment induced cerebral edema and mass effect

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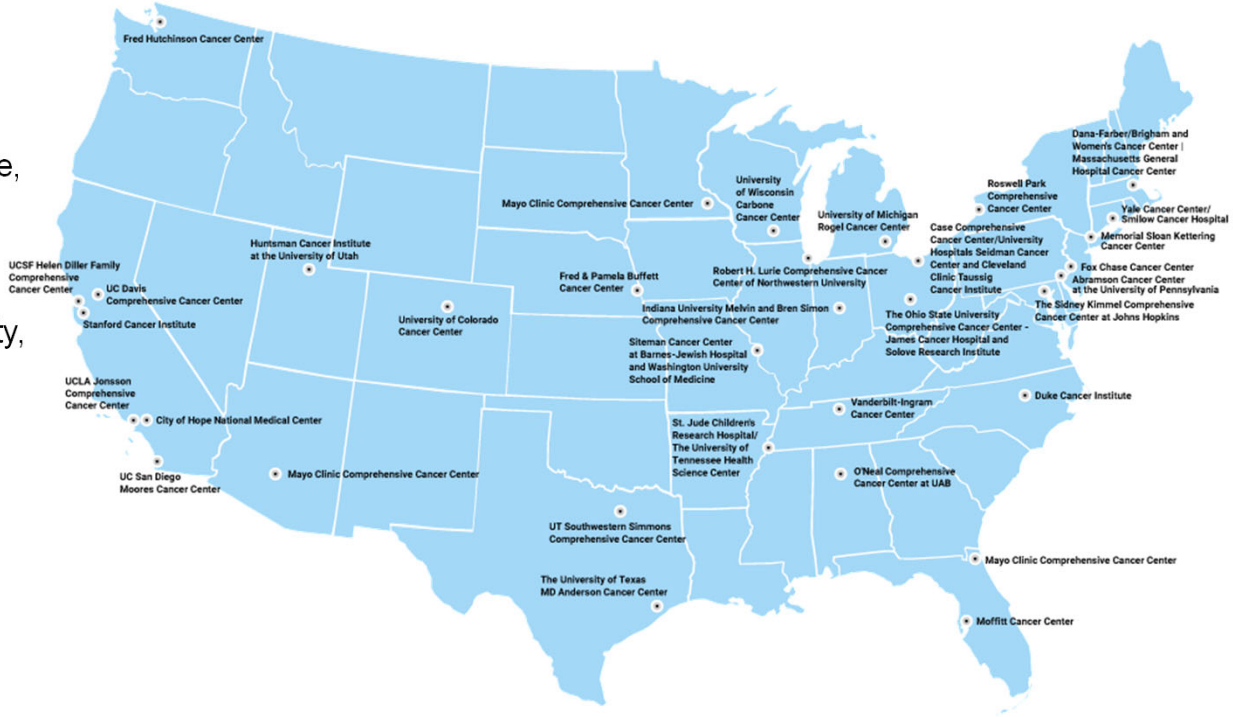

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