Selecting the Optimal Treatment for Brain Metastases

Clinical Practice Today CME

Co-provided by

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Learning Objectives

Upon completion, participants should be able to:

- Understand the benefits, limitations, and indications for use of radiosurgery, neurosurgery, and whole-brain radiation therapy for brain metastases
- Discuss the role of combination and adjuvant therapies in the treatment of metastatic disease
- Explain the individual patient- and disease-related factors that should be considered when planning treatment for brain metastases

Clinical Presentation

Symptom (%)		Sign (%)	
Headache	49	Hemiparesis	59
Altered mental status	32	Cognitive deficits	58
Focal weakness	30	Sensory deficits	21
Ataxia	21	Papilledema	20
Seizures	18	Ataxia	19
Speech difficulty	12	Apraxia	18

- No pathognomic signs/symptoms for brain mets
- Many other etiologies can mimic brain mets (and vice versa)

Halperin EC, et al. Perez and Brady's Principles & Practice of Radiation Oncology. 2013.

Management of Brain Metastases

- Local therapies
  - Surgical resection
  - SRS
- Global therapies
  - WBRT
  - Biochemotherapy? (not established)
- Combined therapies (eg, surgery + WBRT)
- Supportive care alone
- Is it really a met?
  - Close observation vs. biopsy

Kalkanis SN, et al. J Neurooncol. 2010;96:33-43; Gaspar LE, et al. J Neurooncol. 2010;96:17-32.

Outcomes of Surgical Resection for Single Brain Metastasis

Surgical resection + WBRT results in:

- An increased OS
- A longer period of functional independence
- A better quality of life
- Less frequent recurrence at the site of the original metastasis
- Reduction in neurologic death

In a nutshell:

- Surgical resection < surgical resection + WBRT
- Surgical resection + WBRT = SRS + WBRT

Videtic, GM, et al. ACR Appropriateness Criteria, 2014; Kalkanis SN, et al. J Neurooncol. 2010;96:33-43; Patchell RA, et al. JAMA. 1998;280:1485-9.

Optimizing the Therapeutic Ratio in Radiation Therapy

Increase tumor kill

- Do not miss the tumor
- Use maximum tolerated dose
- Treat over as short a time as possible
- Concentrate RT on target
- Use radiosensitizers

Spare normal tissue

- Do not irradiate normal tissue
- Break the dose up into many small fractions
- Extend treatment time
- Spread RT throughout normal tissue
- Use radioprotectants

Kirkpatrick JP, 2014.

Benefits of WBRT vs. SRS

WBRT

- Effective for ≥ 5 mets
- Considered to be the standard of care

SRS

- Less invasive, fewer risks because it involves no cutting
- Spares normal tissue
- Avoids neurocognitive side effects caused by WBRT
- Can start/resume chemotherapy immediately after
- May be effective for up to 10 brain mets

Park HS, et al. Expert Rev Anticancer Ther. 2011;11:1731-8; Jairam V, et al. CNS Oncol. 2013;2:181-93; Yamamoto M, et al. Lancet Oncology. 2014;15:387-95.

Factors Affecting Treatment Choice, Toxicity, and Survival

- Number of mets (1, 2-3, 4+)
- Size of lesion(s) (diameter/volume)
- Location (eloquent?)
- Total intracranial target volume?
- Neurologic deficits
- Age/KPS
- Primary tumor/stage
- RPA class
- Extracranial disease
- Patient's input

Tsao MN, et al. Pract Radiat Oncol. 2012;2:210-25; Jairam V, et al. CNS Oncol. 2013;2:181-93.

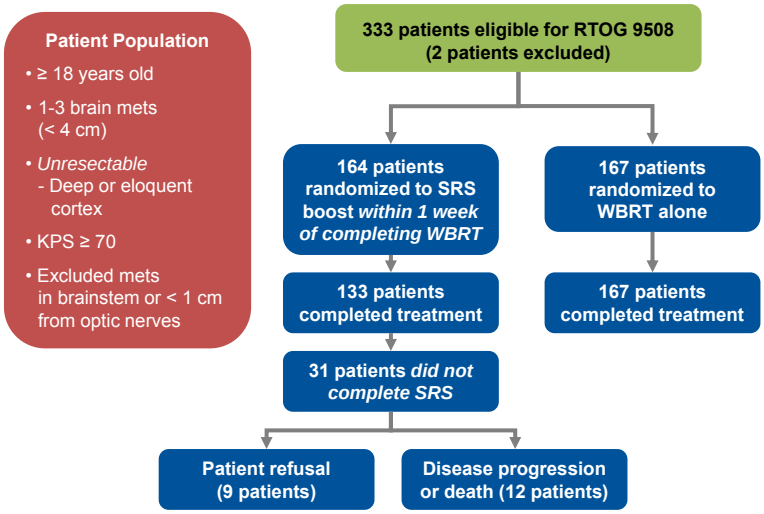
Clinical Guidelines: Initial Management of Multiple Brain Metastases – ASTRO 2012

Treatment options for patients with good prognosis (expected survival ≥ 3 months), surgical resection possible:

Tumor Size	Treatment Options	Evidence Level
≤ 3-4 cm	Surgery + WBRT	1
	SRS + WBRT	1
	SRS alone	1
	Surgery + radiosurgery/radiation boost to the resection cavity with or without WBRT	3
> 3-4 cm	Surgery + WBRT	1
	Surgery + radiosurgery/radiation boost to the resection cavity with or without WBRT	3

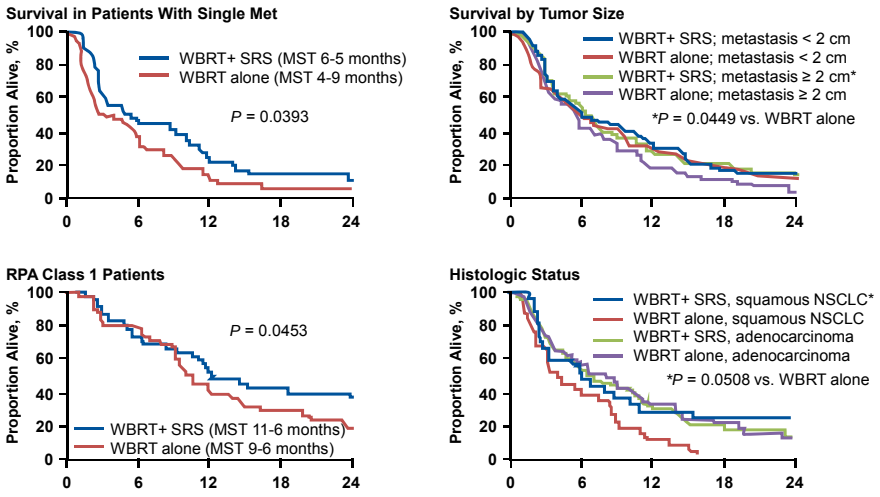
Tsao MN, et al. Pract Radiat Oncol. 2012;2:210-25.

Study Design: RTOG 9508



Andrews DW, et al. Lancet. 2004;363:1665-72.

Results: RTOG 9508



Andrews DW, et al. Lancet. 2004;363:1665-72.

Duke Neurosurgery: Research Question

What is the optimum planning target volume (PTV) in SRS of brain mets?

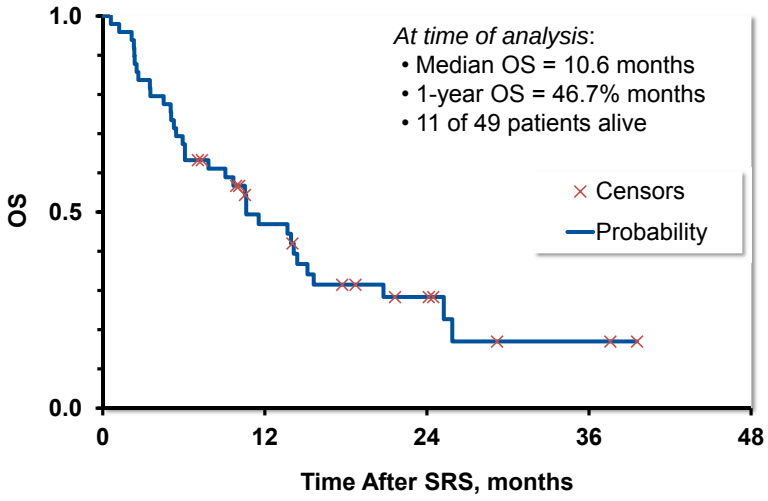
Optimum =

- Minimal morbidity
  - Minimal edema/inflammation/RN
  - Minimal neurocognitive/neurologic deficits

  and
- Maximal control
  - Local control improved
    (ie, fewer recurrences at treated site)
    - Local failure 25% to 40% at 1 year with SRS or surgery alone

Kirkpatrick JP, et al. *Int J Rad Oncol Biol Phys.* 2014; In Press.

Duke Study Results: Overall Survival



Kirkpatrick JP, et al. *Int J Rad Oncol Biol Phys.* 2014; In Press.

Results: Patterns of Failure

- LR: 6.7% risk (K-M) 1 year post SRS
  - 72 lesions with adequate post-SRS imaging
  - **Definite LR was observed in only 3 lesions**
    - 2 biopsy-proven in 1 patient (one each 1- and 3-mm margin)
    - 1 on imaging alone with simultaneous LR and DF
  - No significant difference in 1- vs. 3-mm margins, *P* = 0.51
- Distant brain mets: 46% risk 1 year post SRS
  - Median time to distant recurrence: 9.7 months
- RN alone observed in 6 lesions
  - 5 in the 3-mm group vs. 1 in 1-mm group, log-rank *P* = 0.10
  - 15% vs. 3%, respectively

Kirkpatrick JP, et al. *Int J Rad Oncol Biol Phys.* 2014; In Press.

Take-Home Messages

An SRS boost:

- **Increases survival for patients with:**
  - Single brain met
  - Mets > 2 cm
  - RPA class I
  - Favorable histology (squamous NSCLC)
- **Improves KPS**
- **Produces radiographic responses**
- **Reduces edema and steroid requirements**

Jairam V, et al. CNS Oncol. 2013;2:181-93;
Yamamoto M, et al. Lancet Oncology. 2014;15:387-95;
Andrews DW, et al. Lancet. 2004;363:1665-72.

WBRT, SRS, or SRS + WBRT?

- No consensus has yet emerged
- WBRT + SRS offers best control
- WBRT decreases rate of “distant” brain mets
- Less acute effects with SRS alone
- No clear survival advantage to adding/omitting WBRT
- No clear cognitive advantage/disadvantage to adding WBRT
- Patient preferences/characteristics are key decision factor

Jairam V, et al. CNS Oncol. 2013;2:181-93;
Tsao MN, et al. Pract Radiat Oncol. 2012;2:210-25.

ASTRO “Choosing Wisely” Initiative

Guidance: Do not routinely add adjuvant WBRT to SRS for limited brain mets

- No OS benefit from adding WBRT to SRS in patients with good performance status and brain mets from solid tumors
- Adding WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life
- Patients treated with radiosurgery for brain mets can develop mets elsewhere in the brain; careful surveillance and the judicious use of salvage therapy at the time of brain relapse improves quality of life

ASTRO, Sept. 2014. www.choosingwisely.org/doctor-patient-lists/american-society-for-radiation-oncology.

Emerging Issues

SRS to postoperative resection cavity

- Rationale: decrease LR, salvage RT for distant mets, minimal morbidity
- Patient/tumor selection? Efficacy vs. WBRT?

SRS to large number (> 4) of brain mets

- Technically feasible and “safe”
  - Accurate targeting essential
- Patient/tumor selection? Efficacy vs. WBRT?

Jairam V, et al. CNS Oncol. 2013;2:181-93;
Yamamoto M, et al. Lancet Oncology. 2014;15:387-95.

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