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Brain Metastases: Changing the Paradigm

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SRS is the choice, but:

- Do we need WBRT?
- How many mets can we treat?
- What could be the prescribed dose?
- Does size matter?
- Salvage therapy after SRS?
- Targeted therapies-immunotherapy and SRS?

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- Stereotactic Radiosurgery Plus Whole-Brain Radiation Therapy vs Stereotactic Radiosurgery Alone for Treatment of Brain Metastases
  - Aoyama et al. JAMA, 2006
- Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial
  - Chang et al. Lancet, 2009
- Adjuvant Whole-Brain Radiotherapy Versus Observation After Radiosurgery or Surgical Resection of One to Three Cerebral Metastases: Result of the EORTC 22952-26001 Study
  - Kocher et al. JCO, 2011
- Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial
  - Brown et al. JAMA, 2016

SRS alone vs WBRT + SRS

- WBRT does not improve overall survival
- WBRT improves local and distant control
- WBRT is associated with worse neurocognition

ASTRO releases second list of five radiation oncology treatments to question, as part of national Choosing Wisely® campaign

September 15, 2014

ASTRO
TARGETING CANCER CARE

News Release

Embargoed until 1:15 p.m. PT, Sunday, September 14, 2014

Contact: Michelle Kirkwood
703-286-1600
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Press Office in San Francisco
September 14-17
415-978-3503
415-978-3504

ASTRO releases second list of five radiation oncology treatments to question, as part of national *Choosing Wisely*® campaign

Encourages more detailed conversations between physicians and patients

- **Don't routinely add adjuvant whole brain radiation therapy to stereotactic radiosurgery for limited brain metastases.**

  Randomized studies have demonstrated no overall survival benefit from the addition of adjuvant whole brain radiation therapy (WBRT) to stereotactic radiosurgery (SRS) in the management of selected patients with good performance status and brain metastases from solid tumors. The addition of WBRT to SRS is associated with diminished cognitive function and worse patient-reported fatigue and quality of life. These results are consistent with the worsened, self-reported cognitive function and diminished verbal skills observed in randomized studies of prophylactic cranial irradiation for small cell or non-small cell lung cancer. Patients treated with radiosurgery for brain metastases can develop metastases elsewhere in the brain. Careful surveillance and the judicious use of salvage therapy at the time of brain relapse allow appropriate patients to enjoy the

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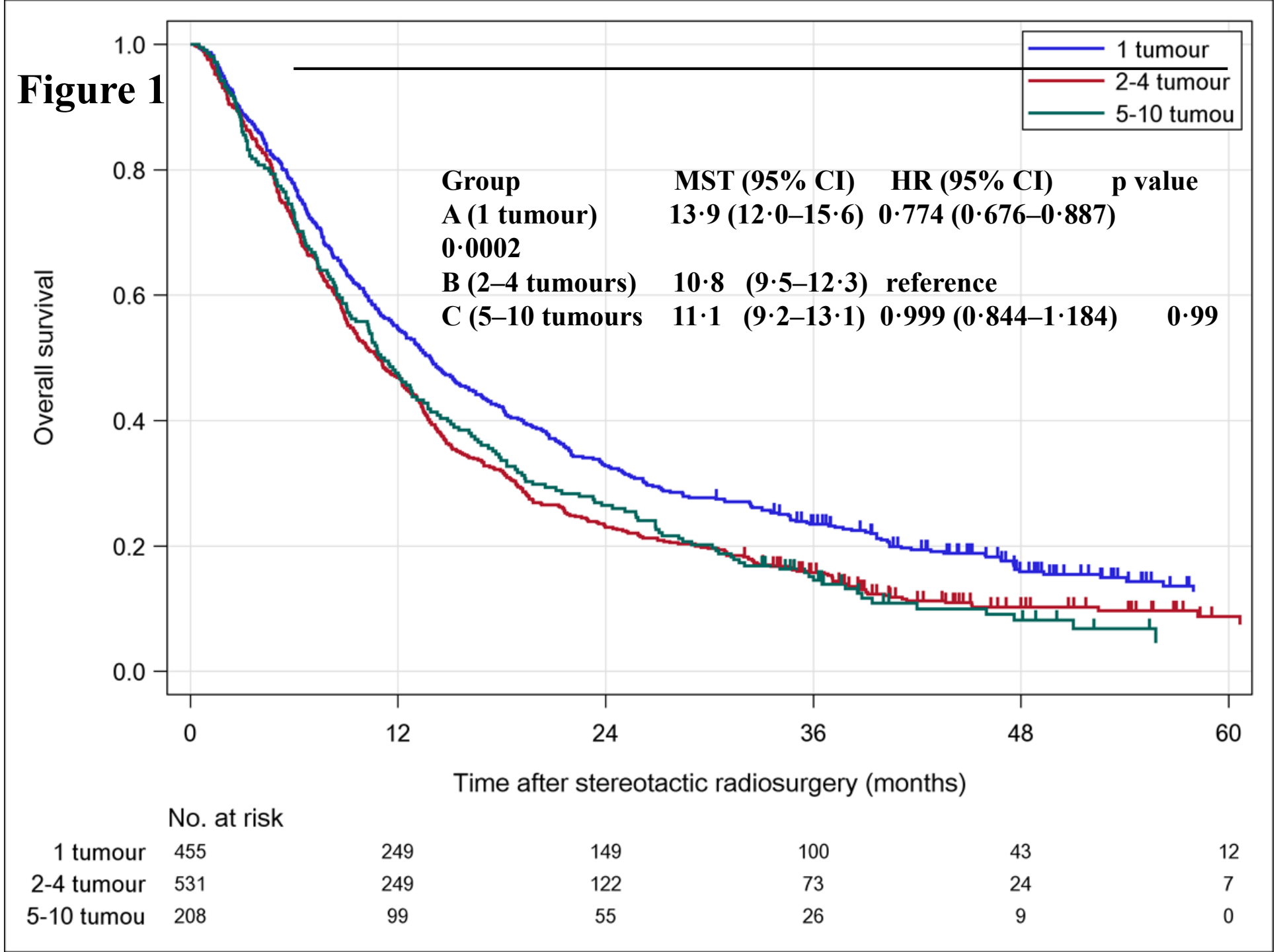
- Yamamoto et al.
- Prospective observational study
- 23 centers
- 1-10 mets
- 1194 patients
- Grup A : 1 met
- Grup B : 2-4 mets
- Grup C : 5-10 mets

Yamamoto et al., Lancet Oncology, 2014

Figure 1


1 tumour
2-4 tumour
5-10 tumou
Group MST (95% CI) HR (95% CI) p value
A (1 tumour) 13·9 (12·0–15·6) 0·774 (0·676–0·887)
0·0002
B (2–4 tumours) 10·8 (9·5–12·3) reference
C (5–10 tumours 11·1 (9·2–13·1) 0·999 (0·844–1·184) 0·99
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
Time after stereotactic radiosurgery (months)
No. at risk
1 tumour 455 249 149 100 43 12
2-4 tumour 531 249 122 73 24 7
5-10 tumou 208 99 55 26 9 0

- 1194 patients
- 1 tumor; 455 patients, median OS 13.9 months
- 2-5 tumors; 531 patients, median OS 10.8 months
- 5-10 tumors; 208 patients, median OS 10.8 months

- 9(%2), 13(%2), 6(%3) patients grade 3-4 side effect

Yamamoto et al., Lancet Oncology, 2014

Not number but volume?

Multivariate Analysis for overall survival

	Volume	Number
Bhatnagar, IJROBP 2006	p=0.002	p=0.3
Likhacheva, IJROBP 2012	p<00.1	p=0.2
Choi, IJROBP 2012	p=0.01	NS
Baschnagel, JNS 2013	p=0.003	p=0.1
Shultz, IJROBP 2015	p<0.01	p=0.1

Yamamoto study

- Largest tumor volume was <10 cm^3, diameter <3cm
- Total tumor ≤15 cm^3

Yamamoto et al., Lancet Oncology, 2014

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SRS Dose (RTOG 90-05)

- Phase I dose escalation study
- To determine the maximum tolerated dose of single fraction SRS in patients previously irradiated primary brain tumors and brain mets.

Table 2. RTOG CNS toxicity criteria

Grade	Definition
1	Mild neurologic symptoms; no medication required
2	Moderate neurologic symptoms; outpatient medication required (e.g., steroids)
3	Severe neurologic symptoms; outpatient or inpatient medication required
4	Life-threatening neurologic symptoms (e.g., uncontrolled seizures, paralysis, or coma); includes clinically or radiographically suspected radionecrosis and histologically proven radionecrosis at the time of an operation
5	Death

Shaw et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final Report of RTOG Protocol 90-05. Int. J. Radiation Oncology Biol. Phys., 47: 2, 291-298.

RTOG 90-05 Results

Table 5. Incidence of Grade 3, 4, and 5 CNS toxicity by tumor size and treatment arm

Incidence of Grade 3, 4, and 5 CNS Toxicity						
				% of Patients With Toxicity		
Tumor size*	Arm	Dose	No. of patients	Acute	Chronic	Total
≤ 20 mm						
	1	18 Gy	12	0	8	8
	4	21 Gy	18	0	11	11
	7	24 Gy	10	0	10	10
21–30 mm						
	2	15 Gy	15	7	7	13
	5	18 Gy	15	0	20	20
	8	21 Gy	13	8	31	38
	11	24 Gy	12	33	25	58
31–40 mm						
	3	12 Gy	21	5	5	10
	6	15 Gy	22	0	14	14
	9	18 Gy	18	17	33	50

* Maximum tumor diameter.

Lesion diameter	Maximum Tolerance Dose
≤ 20 mm	24 Gy
21-30 mm	18 Gy
31-40 mm	15 Gy

Shaw et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final Report of RTOG Protocol 90-05. Int. J. Radiation Oncology Biol. Phys., 47: 2, 291-298.

Yamamoto study

- 22 Gy <4 cm^3 and 20 Gy to others

Yamamoto et al., Lancet Oncology, 2014

Table 2. Dose selection algorithm accounting for treatment volume, number of metastases, tumor histology and prior WBRT.

Planning Treatment Volume	RTOG 90-05	Number of Metastases	Radioresistant / Prior WBRT	Radioresistant / No Prior WBRT	Radiosensitive / Prior WBRT	Radiosensitive / No Prior WBRT
		1-4	22 Gy	22 Gy	22 Gy	22 Gy
0-4.5 cc	24 Gy	5-10	20 Gy	20 Gy	20 Gy	20 Gy
		1-4	22 Gy	22 Gy	20 Gy	22 Gy
4.6-7.0 cc	18 Gy	5-10	20 Gy	20 Gy	18 Gy	20 Gy
		1-4	20 Gy	20 Gy	20 Gy	20 Gy
7.1-8.5 cc	18 Gy	5-10	18 Gy	20 Gy	18 Gy	18 Gy
		1-4	20 Gy	20 Gy	18 Gy	20 Gy
8.6-11.0 cc	18 Gy	5-10	18Gy	18 Gy	18 Gy	18 Gy
		1-4	20 Gy	20 Gy	18 Gy	20 Gy
11.1-14.0 cc	18 Gy	5-10	16 Gy	18 Gy	16 Gy	18 Gy
		1-4	18 Gy	18 Gy	16 Gy	18 Gy
14.1-22.0 cc	15 Gy	5-10	16 Gy	16 Gy	16 Gy	16 Gy
		1-4	16 Gy	16 Gy	15 Gy	16 Gy
22.1-34.0 cc	15 Gy	5-10	16 Gy	16 Gy	15 Gy	16 Gy

A contemporary dose selection algorithm for stereotactic radiosurgery in the treatment of brain metastases – An initial report. Rovel et al. Journal of Radiosurgery and SBRT, 2016. Yale University

We still need to define the best prescription doses according to:

- Tumor volume
- Histopathology
- Extracranial disease status
- Medical treatment

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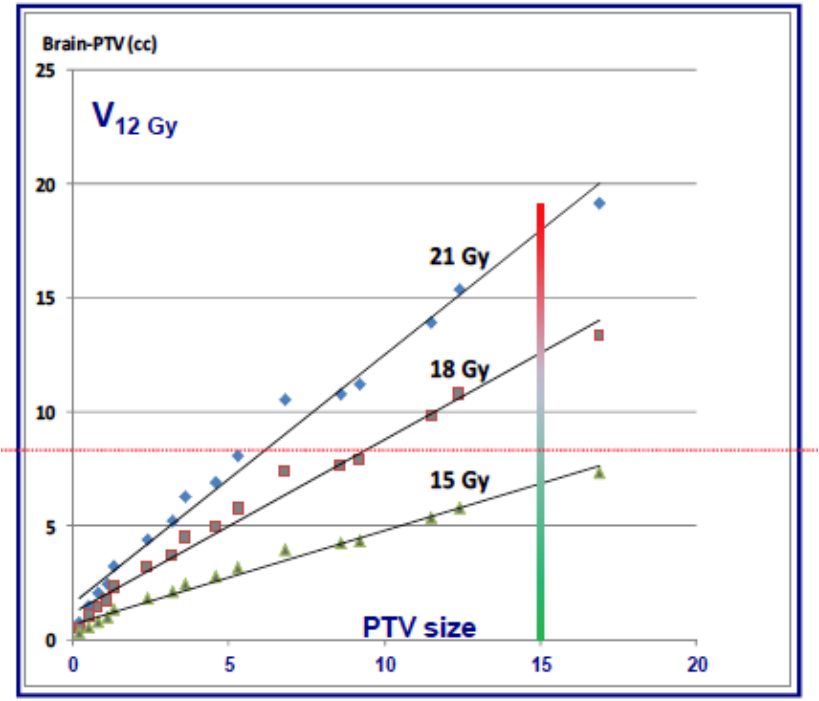
You can not increase the total dose

- 2 cm 4.8 cm^3
- 2.5 cm 9.2 cm^3
- 3 cm 15.6 cm^3
- 3.5 cm 24.2 cm^3



Minniti et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiation Oncology 2011

Fractionation

- 27-30 Gy in 3 fx
- 31-35 Gy in 5 fx
- Effective and tolarable

Murai et al. Fractionated Stereotactic Radiotherapy using Cyberknife for the Treatment of Large Brain Metastases: A Dose Escalation Study. Clinical Oncology, 2014

Single vs multifraction SRS: Meta-analysis of 24 trials

- In the treatment of large brain metastases with radiosurgery
- MF-SRS may offer a relative reduction of radionecrosis
- MF-SRS maintains or improves relative rates of 1-year LC compared to SF-SRS

Lehrer et al. Single versus Multifraction Stereotactic Radiosurgery for Large Brain Metastases: An International Meta-analysis of 24 Trials. IJROBP, 2019.

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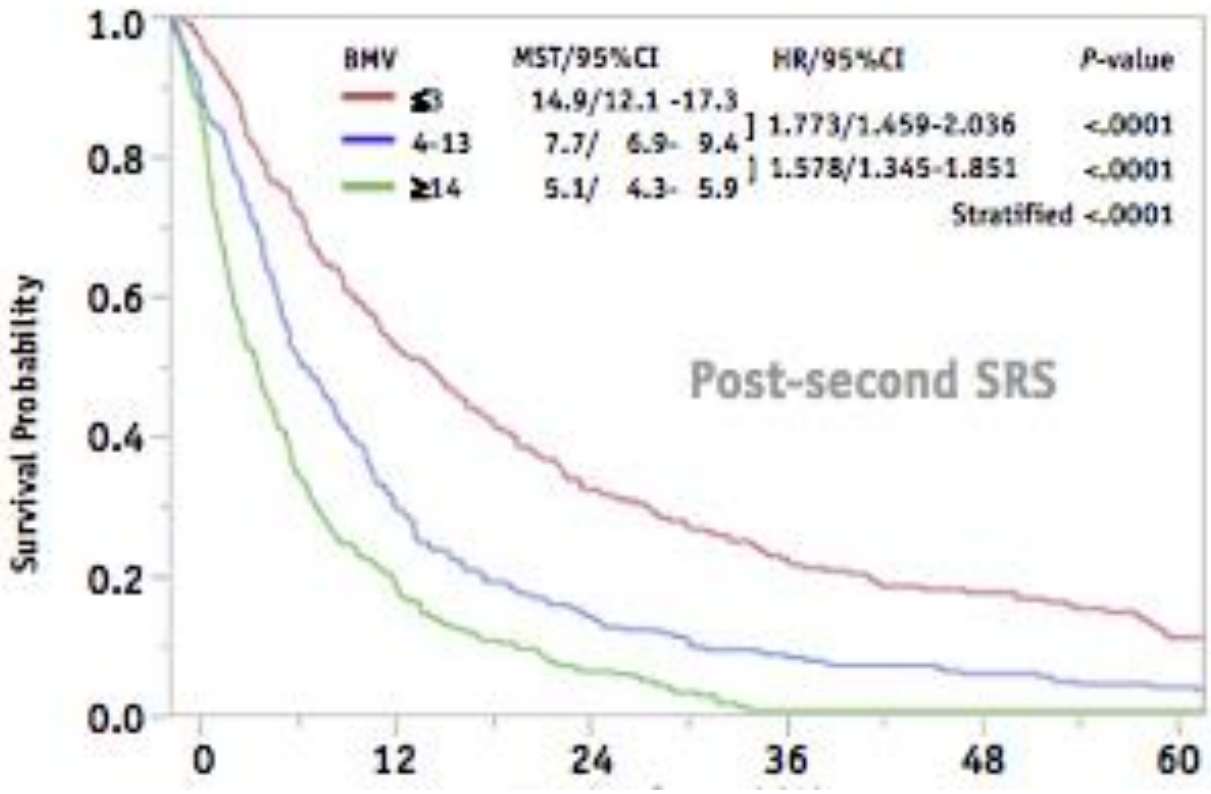
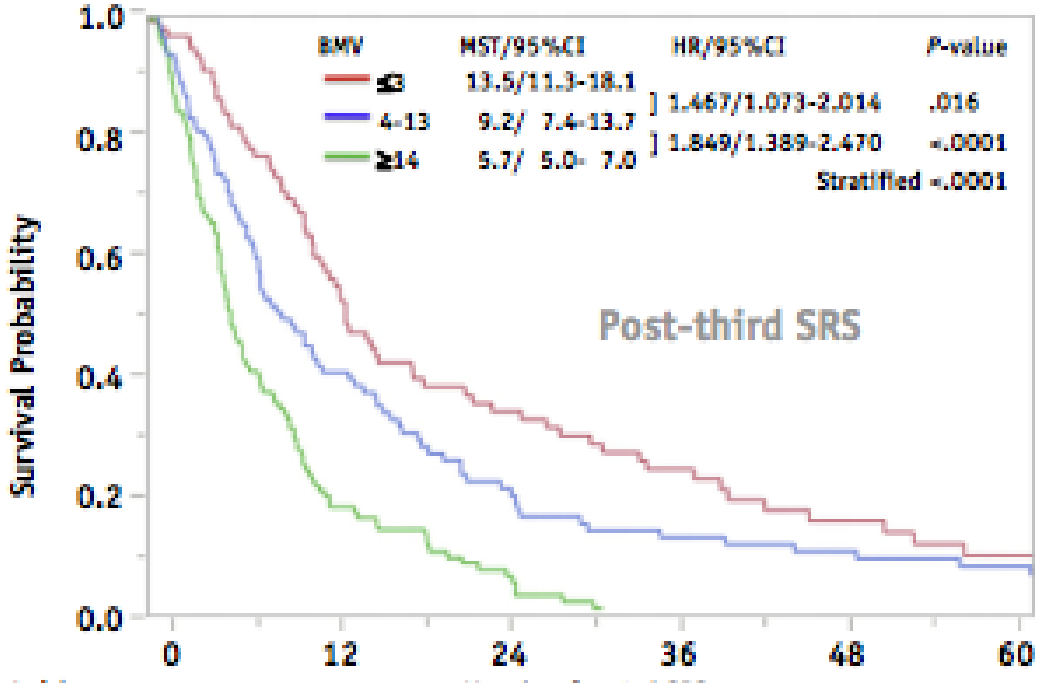
- A simple grading system is developed
- Brain metastasis velocity (BMV), which is specifically applicable to salvage treatment of newly arising tumors after SRS alone
- The BMV score is the cumulative number of new BMs developing after the first SRS divided by the time (in years) since the initial SRS

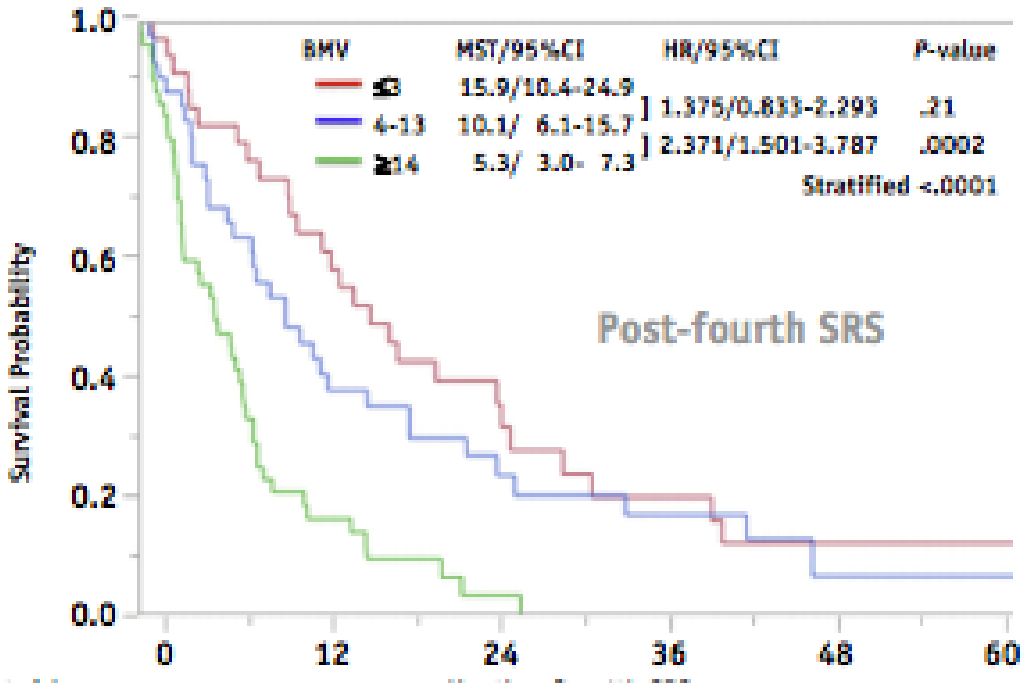
Farris M et aL. Brain metastasis velocity: A novel prognostic metric predictive of overall survival and freedom from whole-brain radiationtherapy after distant brain failure following upfront radiosurgery alone. IJROBP 2017.

- Japanese retrospective cohort study
  - 833 patients who underwent second SRS
  - 250 third SRS
  - 88 fourth SRS
- Analyzed patients by brain metastasis velocity (BMV) = cumulative # of brain mets developed/time since initial SRS



Yamamoto M et al. Validity of a Recently Proposed Prognostic Grading Index, Brain Metastasis Velocity, for Patients With Brain Metastasis Undergoing Multiple Radiosurgical Procedures. IJROBP 2019





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Checkpoint inhibitors for asymptomatic melanoma brain metastasis

- Checkmate 204, phase II multicenter single arm study
- Nonirradiated brain metastasis (tumor diameter, 0.5 to 3 cm)
- No neurologic symptoms
- Nearly 75% had 1-2 lesions
- Nivolumab plus ipilimumab for up to four doses
- Followed by nivolumab until progression or unacceptable toxic effects
- The rate of intracranial clinical benefit was 57%
  - complete response was 26%,
  - partial response was 30%
  - stable disease for at least 6 months was 2%.

Tawbi et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. NEJM, 2018

Checkpoint inhibitors for symptomatic melanoma brain metastasis

- Outcomes are inferior with checkpoint inhibitors alone
- Intracranial response rate was 16.7%
- Timing of radiation is still unanswered

Tawbi et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. NEJM, 2018

NSCLC Brain Metastases and Checkpoint inhibitors

- Yale phase 2 study – pembrolizumab
- Asymptomatic untreated brain mets > 2cm
- Response rate (CR + PR) among 18 patients - 33%
- There might be a role for systemic immunotherapy in patients with asymptomatic untreated or progressive brain metastases

Goldberg et al. Pembrolizumab for Patients With Melanoma or Non-Small-Cell Lung Cancer and Untreated Brain Metastases: Early Analysis of a Non-Randomised, Open-Label, Phase 2 Trial. Lancet Oncology, 2016

Checkpoint inhibitors + SRS

- Large retrospective series suggest superior outcomes with concurrent SRS and immune checkpoint inhibitors vs delayed radiation
- Lehrer Meta-analysis
- 534 patients, 1570 lesions (mostly melanoma)
  - 1-year OS (64.6% vs 51.6%, $p<0.001$) and
  - regional brain control (38.1% vs 12.3%, $p=0.049$),
  - Trend in LC (89.2% vs 67.8%, $p=0.09$)

Lehrer et al. Treatment of Brain Metastases With Stereotactic Radiosurgery and Immune Checkpoint Inhibitors: An International Meta-Analysis of Individual Patient Data. Radiotherapy and Oncology, 2019.

Sequencing with SRS

- Optimal sequencing to minimize toxicity: unanswered question

Targeted agents for brain metastases

- Lung adenocarcinoma
  - EGFR mutant
  - ALK positive
- Melanoma
  - BRAF mutated

- 3rd generation TKI, Osimertinib is more effective for asymptomatic brain metastases than cytotoxic chemotherapy and 1st generation EGFR TKI’s
- 2nd and 3rd generation ALK/ROS1 inhibitors yield promising CNS control superior to 1st generation

EGFR-TKI therapy and SRS sequencing

- Retrospective study
- 31 pts received SRS
- 176 pts., 61 % upfront TKI, 39 % upfront local therapies
- Upfront LT group showed significantly better OS compared with TKI group
  - 35 vs 23 months

Miyawaki et al. Optimal sequence of local and EGFR-TKI therapy for EGFR-mutant non-small cell lung cancer with brain metastases stratified by number of brain metastases. IIJROBP 2019.

- Pooled multi-institutional retrospective series suggest **upfront SRS** in TKI- naïve patients is **associated with improved OS** vs delaying radiation until progression
- Developing brain metastases on TKI is associated with worse OS

- SRS in brain metastases
  - Mostly first choice
  - WBRT and surgery could be used in selected cases
  - Dose selection is important
  - Could be used in large, multiple and radioresistant metastases
  - New systemic agents are promising
- Brain metastasis is not a single disease

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