Treatment approach of multi-metastases brain radiosurgery: *A clinician's perspective*

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University of Rochester

Multiple brain metastases

- What is 'multiple' with respect to brain metastases ?
  - **2+** *(literal definition)* ?
  - **>4** *(definition for which relatively few studies exist for SRS alone)* ?
  - **>10** *(definition for which many would consider whole brain radiotherapy – WBRT – vs. SRS alone)* ?

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Multiple brain metastases

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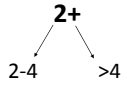


Multiple brain metastases

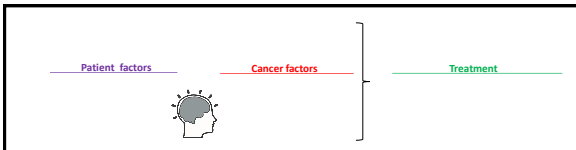
- What is multiple with respect to brain metastases ?

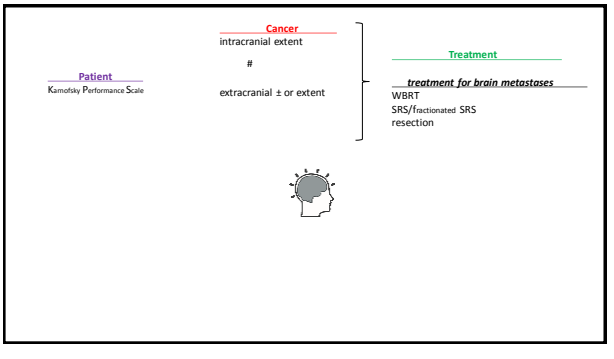
2+

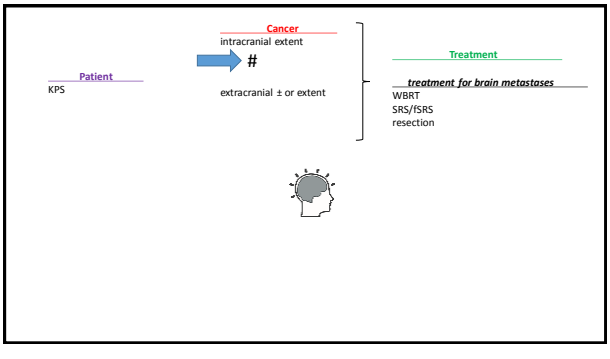
2-4

For SRS alone:
- Plenty of retrospective data
- Recent Phase III data

>4 – For SRS alone: limited data
- *primarily retrospective and single arm prospective*







National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2019

"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.

ASTRO Model Policy for SRS

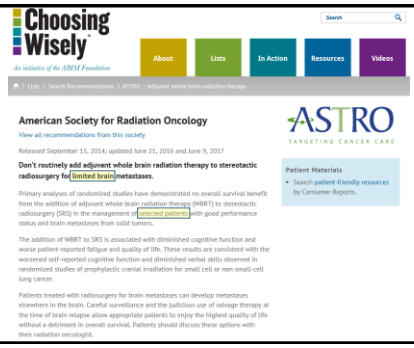
Indications and Limitations of Coverage and/or Medical Necessity

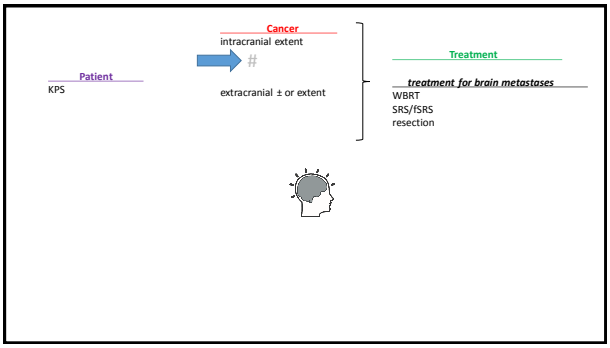
Indications for Coverage:

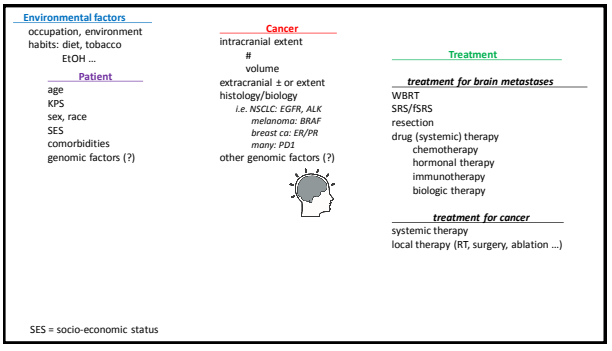
7. Metastatic brain, independent of the number of lesions if other positive clinical indications exist, with stable systemic disease, Karnofsky Performance Status 40 or greater (and expected to return to 70 or greater with treatment), and otherwise reasonable survival expectations, OR ECOG Performance Status of 3 or less (or expected to return to 2 or less with treatment).

Updated in 2014

ASTRO Choosing Wisely






Environmental factors
occupation, environment
habits: diet, tobacco
EtOH …
Patient
age
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sex, race
SES
comorbidities
genomic factors (?)
Cancer
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#
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i.e. NSCLC: EGFR, ALK
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breast ca: ER/PR
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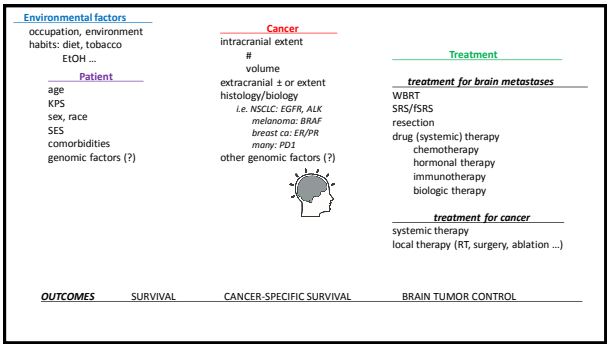
other genomic factors (?)
Treatment
treatment for brain metastases
WBRT
SRS/fSRS
resection
drug (systemic) therapy
chemotherapy
hormonal therapy
immunotherapy
biologic therapy
treatment for cancer
systemic therapy
local therapy (RT, surgery, ablation …)
SES = socio-economic status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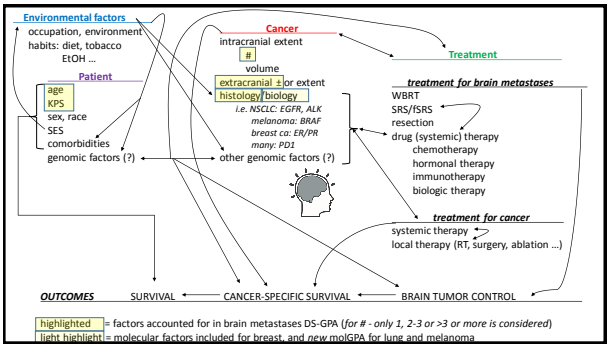
CANCER-SPECIFIC SURVIVAL
BRAIN TUMOR CONTROL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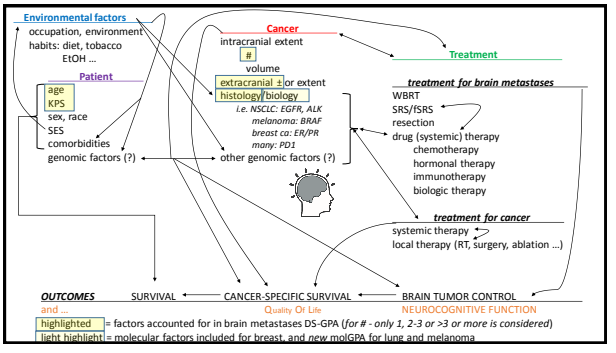
light highlight = molecular factors included for breast, and new molGPA for lung and melanoma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and …
Quality Of Life
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What are the data on SRS alone vs. SRS+WBRT for multiple metastases ?

4 RCTs of SRS alone vs. SRS+WBRT

Study 1st author	Patients	RCT arms	1-year local recurrence	1-year distant recurrence	Rate of salvage therapy	Rate of salvage WBRT	Median survival (M)
Aoyama (Japan) 2006	132 patients with 1-4 metastases, all ≤3 cm	SRS WBRT+SRS	**28%** 11% (p=0.002)	**64%** 41% (p=0.003)	**43%** 16% (p<0.001)	16% 0%	8.0 7.5 (p=0.42)
Chang (MDACC) 2009	58 patients with 1-3 brain metastases	SRS WBRT+SRS	**23%** 0% (p=0.01)	**55%** 27% (p=0.02)	**87%** 7%	33% 0%	15.2 5.7 (p=0.003)
Kocher (EORTC) 2011	359 patients with 1-3 brain metastases	SRS or resection WBRT+ SRS *or* WBRT+resect.	**~31%** **~57%** ~19% ~27% (p<0.003)*	**~48%** **~42%** ~33% ~23% (p<0.001)*	**} 51%** } 16%	} 31% } 3%	} 10.9 } 10.7 (NS)
Brown (Alliance) 2016	213 patients with 1-3 metastases, all ≤3 cm	SRS WBRT+SRS	**23%** 10% (p=0.003)	**30%** 8% (p<0.001)	**32%** 8% (p<0.001)	16% 1%	10.4 7.4 (p=0.92)

* p value of addition vs. omission or WBRT

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48%, 57%, 81% and 52% of patients in these 4 studies (respectively) had only 1 metastasis
* p value of addition vs. omission or WBRT

Omission of WBRT in patients with 1-4 brain metastases

- increases **local tumor recurrence** (~23-31% vs. 0-19% @ 1Y)
- increases **distant brain recurrence** (~30-64% vs. 8-41% @1Y)
- increases **rate of salvage treatment** (~32-87% vs. ~7-16%)

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- does NOT detriment **overall survival**

4 RCTs of SRS alone vs. SRS+WBRT

Study 1st author	+ vs. - WBRT
Aoyama (Japan) 2006	- **MMSE**: average duration until deterioration 7.6 vs. 16.5 months **(p=0.05)** - KPS: preserved at 1Y in 34% vs. 27% (p=0.53) - neurologic function: preserved in 72 vs. 70% (p=0.99)
Chang (MDACC) 2009	- **HVLT–R**: drop in total recall (64% vs. 20%) at 4 months **(96% confidence in difference)** - *Battery of other cognitive and QOL assessments performed as well*
Kocher (EORTC) 2011	- **WHO–PS decline** (to a score of >2): 9.5 vs. 10 months (p=0.71) - **QOL –** multiple domains significantly worse with WBRT
Brown (Alliance) 2016	- **cognitive function** (battery of tests): deterioration at 3 months 92% vs. 63% **(p<0.001)** - **FACT-BR:** worse at 3 months (p=0.03) with WBRT - **ADLs**: similar

MMSE = mini mental status examination
KPS = Karnofsky Performance Scale
WHO PS = World Health Organization Performance Score
HVLT = Hopkins Verbal Learning Test (test of recall)
FACT-BR = Functional Assessment of Cancer Therapy–Brain
ADL = Activities of Daily Living

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- increases **distant brain recurrence** (~30-64% vs. 8-41% @1Y)
- increases **rate of salvage treatment** (~32-87% vs. ~7-16%)
- does NOT detriment **overall survival**
- less detriment in **neurocognitive function**

SRS alone for >4 metastases ?

SRS alone for >4 metastases

Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues

Arjun Sahgal, Mark Ruschin, Lijun Ma, Wilko Verbakel, David Larson, and Paul D. Brown

- Systematic (PRISMA) literature search 1947 through 2015
  for studies with ALL or SUBGROUP or patients having >4 metastases
  → 3,084 articles →→
  - **10** articles *(all but 1 were retrospective)*
    - *ALL patients had >4 metastases treated with SRS*
      - 5-37 metastases (mean range from 6-17)
      - Total target volume 3.2-10.9 cc
  - *Additional 5 studies excluded for not reported distant brain control*

Sahgal A, et al. Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues. Neuro Oncol. 2017;19(S2):ii2-15.

SRS alone for >4 metastases

Author (year)	Range of Metastases/ Total Volume/ Number of Patients	Key Patient Inclusion Criteria	Median Follow-up	Local Recurrence	Distant Brain Failure (DBF)/ Time to DBF	Overall Survival
Yamamoto et al[27] (2014) *Prospective observational*	5–10 mets (median 6)/ mean = 3.54 cc/208	No single met >3 cm or 10 cc Cumulative tumor volume ≤15 cc KPS ≥70 (100% no prior WBRT)	12 mo	1 y = 6.5% 2y = 9.8%	1 y = 63.8% 2 y = 72%/ median = 8.04 mo	Median = 10.8 mo
Salvetti et al[13] (2013)	5–15 (median 7)/ median per patient = 6.12 cc/ 96	Histology other than small cell or unknown primary KPS≥70 (53% no prior WBRT)	4.1 mo	1 y = 15.2% 2 y = 25.1%	Crude: 41.0% /NR	5–9 mets = median 4.8 mo, 10–15 mets = median 3.4 mo
Rava et al[28] (2013)	10–34 (mean 11)/NR/53	KPS≥70 (36% no prior WBRT)	NR	Crude: 13.2%	1 y = 90%/ median = 3 mo	median = 6.5 mo
Mohammadi et al[25] (2012)	5–20 (median 6)/ median = 3.2 cc/178	KPS≥70 (46% no prior WBRT)	6.2 mo	Crude: 3%	Crude: 40%/ median = 2.1 mo	median = 6.7 mo
Grandhi et al[26] (2012)	10–28 (mean 13.2)/ median = 4.86 cc/61	77% KPS 90–100 (377% no prior WBRT)	4 mo	1 y = 58.3%	1 y = 726%/ median = 3 mo	Median = 4 mo
Lee et al[17] (2011)	4–14/NR /36	Median KPS 90 (range, 60–80) (80.6% no prior WBRT)	4.5 mo	9 mo = 15.8%	Crude = 22.2%/ median = 4 mo	Median: 4.5 mo
Chang et al[29] (2010)	Group 2: 6–10/NR /58 Group 3: 11–15 /NR/17 Group 4: >15/NR/33	KPS≥70 RPA 1 or 2 (Group 4, 42.4% had prior WBRT)	*Group 2: 10.7 mo Group 3: 12.3 mo Group 4: 8 mo	*Group 2: 1 y = 83% Group 3: 1 y = 92% Group 4: 1 y = 89% (Group 4, 36.8% of the 519% developing distant mets were within 3 mo)	*Group 2: 1 y = 472%/ median = 8.8 mo Group 3: 1 y = 53.1%/ median = 5.3 mo Group 4: 1 y = 80.3%/ median = 5.0 mo	*Group 2: 1 y = 83% Group 3: 1 y = 92% Group 4: 1 y = 88%
Kim et al[30] (2008)	10–37 (mean 16.6)/mean 10.9 cc/28	KPS≥70 (68% prior/ adjuvant WBRT)	NR	6 mo = 20.8%	6 mo = 26.9% /NR	Median = 7.8 mo
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Nam et al[31] (2005)	4–10/NR/46	Not specified for this cohort	Mean = 13.3 mo	1 y = 30.5%	1 y = 78.1%/NR	Median = 5.4 mo

Sahgal A, et al. Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues. Neuro Oncol. 2017;19(S2):ii2-15.

SRS alone for >4 metastases

- **1-year local recurrence**: 6.5 - 58.3%
  - *"**heterogeneity** in cohorts with respect to histology and definition of local tumor control"*
  - *"**consistent** with the literature overall"*
- **Distant brain recurrence**: 22 - 90%
  - *"**heterogeneity** in primary tumor type and definition of extracranial disease control status"*
    - Prior WBRT in *some* patients
- **Median survival**: 3.4 - 13 months
  - Favorable factors: better RTOG RPA score, ↑*KPS*, favorable histology (i.e. breast), *controlled extracranial tumor, ↓age*

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SRS alone for multiple metastases : JLGK0901 study

- **Prospective observational study** *(2009-2012)*
  - 1-10 metastases
    - all <10 ml and <3 cm
    - Cumulative volume ≤15 ml
  - 1 metastasis (n=455)
  - 2-4 metastases (n=531)
  - 5-10 metastases (n=208) -- *included in Sahgal review*

Yamamoto et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014 Apr;15(4):387-95. JLGK - *Japanese Leksell Gamma Knife*

SRS alone for multiple metastases : JLGK0901 study

1 vs. 2-4 vs. 5-10 metastases groups :

- **OS:** greater for 1 vs. 2-4 (median 13.9 vs. 10.8 M, p=0.0004)
  2-4 similar to 5-10 *(HR=0.97, p=0.78) – median 10.8 M for both*
- **Neurologic death** similar across groups (p=0.27), and ≤10%,
- **LC** similar (p=0.78) across subgroups (10-16%)
- **Distant brain metastases** 48% for 1 metastasis
  - Similar for 2-4 and 5-10 metastases (63 and 69%)
  - **Salvage WBRT** used in ~10%
  - **Savage SRS** used in 40%

need to follow patients with serial brain MRI

Yamamoto et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol. 2014 Apr;15(4):387-95.

SRS alone for multiple metastases: lesion number

Study	# patients	# lesions	Outcomes analyzed by number of metastases
Bhatnagar (2006/2007) *UPMC*	205	4-18	**OS**: number of metastases not significant **(p=0.33)** **RPA**: worse OS subgroup: total treatment volume >7 cc and >7 metastases
Serizawa (2010) *Japan*	1,508	1-10	**OS**: 1 vs. 2-4 **(**HR=0.70; **p<0.0001)** 2-4 vs. 5-10 (HR=1.12; p=0.10)
Serizawa (2012) *Japan*	2,246	1-10+	**need for salvage therapy:** >10 > 5-10 metastases **(p=0.023)**
Yamamoto (2013) *Japan*	2,553	1-89	Net tumor volume 1-4 vs. 5+ metastases - **OS: worse** in 5+ group **(**HR 1.18, **p=0.01)** - **neurologic survival** (without neurologic death): similar (p=0.77) - **salvage therapy:** similar in both groups
JLGK0901 (2014) *Japan*	1,194	1-10	**OS**: 1 vs. 2-4 (HR=0.76; **p=0.0004**) 2-4 vs. 5-10 (HR=0.97; p=0.78)
Ali (2017) *Japan & Australia*	5,750	1-10+	**OS**: 1 vs. 2-4 (HR=0.92; **p=0.010)** 2-4 vs. 5-10 (HR=0.95; p=0.17) 5-10 vs. >10 (HR=0.91; **p=0.025**) 2-10 vs. >10 (HR=0.88; **p=<0.001**)

With SRS alone for one or multiple brain metastases

- Survival outcomes: - better with 1 metastasis (vs. >1)
  - similar across patients with 2-10 metastases
  - worse with >10 metastases
- CNS distant control: worse >10 metastases

SRS alone for 1 or multiple metastases: lesion volume

Study	# patients	# lesions	Outcomes analyzed by tumor volume
Bhatnagar (2006/2007) *UPMC*	205	4-18	**OS**: **treatment volume** was the most significant predictor (**p=0.002**) **RPA**: best OS subgroup: total **treatment volume <7 cc** and <7 metastases
Serizawa (2012) *Japan*	2,246	1-10+	**Net tumor volume >15 cc**, worse (**p<0.0001**) - **OS** - **neurologic survival** (without neurologic death) - **qualitative survival** (without impaired ADL) ↑lesion volume → ↑**tumor progression**
Yamamoto (2013) *Japan*	2,553	1-89	**OS: cumulative tumor volume of >10 cc** (HR>1.4, **p<0.001** for all patients, and subgroups with 1-4 vs. 5+ mets)
JLGK0901 (2014) *Japan*	1,194	1-10	**maximum tumor volume** (**≥1.6** vs. <1.6 cm) **cumulative tumor volume** (**≥1.9** vs. <1.9 ml)
Ali (2017) *Japan & Australia*	5,750	1-10+	**OS**: **cumulative intracranial volume**: HR of 1.015 per cc (**p<0.001**).

adverse factors for **OS** on univariate but not multivariate analyses

With SRS alone for multiple brain metastases

- Survival outcomes: - better with 1 metastasis (vs. >1)
  - similar across patients with 2-10 metastases
  - worse with >10 metastases
  - *worse with greater net GTV*
- CNS distant control: worse >10 metastases

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Future study for those with 4+ brain metastases

- Phase II studies of SRS alone
- Phase III studies of SRS alone vs. WBRT (±SRS)

Phase II

Study group	Study #	# patients	Eligibility	Study arms	Primary outcomes
UT Southwestern	NCT03508752 *(Phase I/II)*	45	6+ metastases all <4cm	SRS	Cognition (HVLT-R)
MDACC	NCT01644591	49	4+ metastases from melanoma	SRS	Local control Cognition

Randomized

Study group	Study #	# patients	Eligibility	Study arms	Primary outcomes
MDACC	NCT01592968 *(enrolling)*	100	4-15 metastases all <3.5 cm	- WBRT - SRS	Local control Cognition (HVLT-R)
NAGKC 12-01	NCT01731704	*closed before accrual*	≥5 metastases All ≤10 cc net GTV≤15 cc	- WBRT - SRS	Cognition QOL
Netherlands	NCT02353000 *(closed … for now ?)*	260	4-10 metastases all <2.5 cm net GTV≤30 cc	- WBRT - SRS	QOL
Dana Farber Cancer Inst.	NCT03075072 *(enrolling)*	196	5-20 metastases	- WBRT (with or without hippocampal sparing) - SRS	QOL
Canadian Cancer Trials Group/NRG	NCT03550391 *(enrolling)*	206	5-15 metastases all <2.5 cm	- WBRT (w/hippocampal sparing) + memantine - SRS	OS Neuro-cogn. PFS
Sunnybrook Health Sciences Centre	NCT03775330 *(enrolling)*	125	5-20 metastases (allow up to 30)	- SRS + WBRT - SRS	Cognition (HVLT-R)

Future study for those with 4+ brain metastases

- Phase II studies of SRS alone
- Phase III studies of SRS alone vs. WBRT (±SRS)
- Phase II/III studies of systemic therapy
  - ALK-rearranged NSCLC
  - EGFR mutant NSCLC
  - BRAF-mutated melanoma
  - Solid cancers with high expression of PDL1

Take home points

- SRS alone for *appropriately selected* patients with:
  - 2-4 brain metastases: is an accepted standard based on level 1 evidence
  - >4 brain metastases: is emerging as an accepted standard
  - >10 brain metastases: is arguably investigational, though perhaps warranted in patients with low volume burden disease

Omission of WBRT in patients with 1-4 brain metastases*

- increases **local tumor recurrence** (~23-31% vs. 0-19% @ 1Y)
- increases **distant brain recurrence** (~30-64% vs. 8-41% @1Y)
- increases **rate of salvage treatment** (~32-87% vs. ~7-16%)
- does NOT detriment **overall survival**
- less detriment in **neurocognitive function**

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