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Frontiers in Radiosurgery: Brain Metastases

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Disclosures:

ACCURAY: Honoraria for presentations, travel expenses, project funding

Brain Metastases (BM): General Facts

increasing incidence for BM:

- improved detection by imaging
- early screening
- from renal cell-, colorectal-, ovarian carcinoma
- improved systemic therapy => longer survival
- generally still poor prognosis, dependent on
    - age, KPS, total intracranial tumor volume, status of systemic disease, GPA score *(including histological / molecular features)*

Kraft 2019, Lam 2014, Nieder 2011, Tabouret 2012, Langer 2005 and other Authors

Level 1 evidence for treatment BM

- SRS + WBRT show no benefit of on overall survival
- SRS + WBRT vs. SRS alone have equal rate of neurological death
- adjuvant WBRT improves distant control
- SRS provides better local control
- more salvage therapy after SRS alone
- close follow-up when SRS alone
- impact on cognitive functioning and quality of life related to WBRT
- WBRT reduces local failure after resection

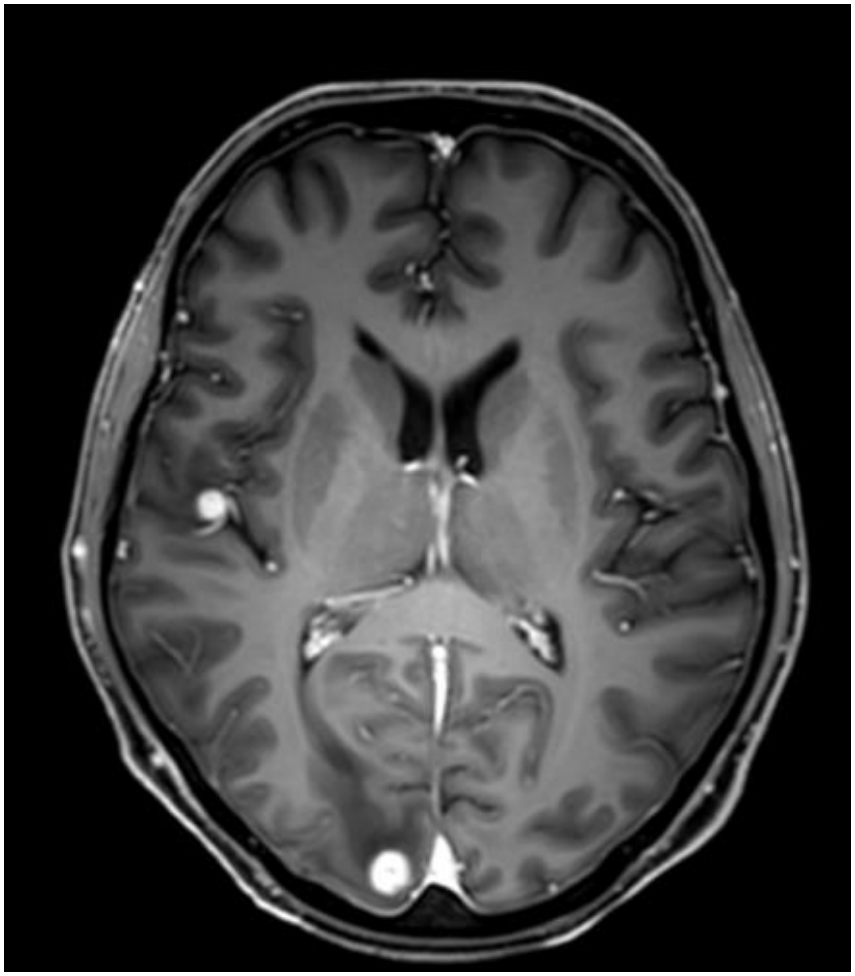
Aoyama 2004, Kocher 2011, Chang 2009, Soffietti 2013, Nieder 2011, Kondziolka 1999, Andrews 2004, Knisely 2011 and other Authors

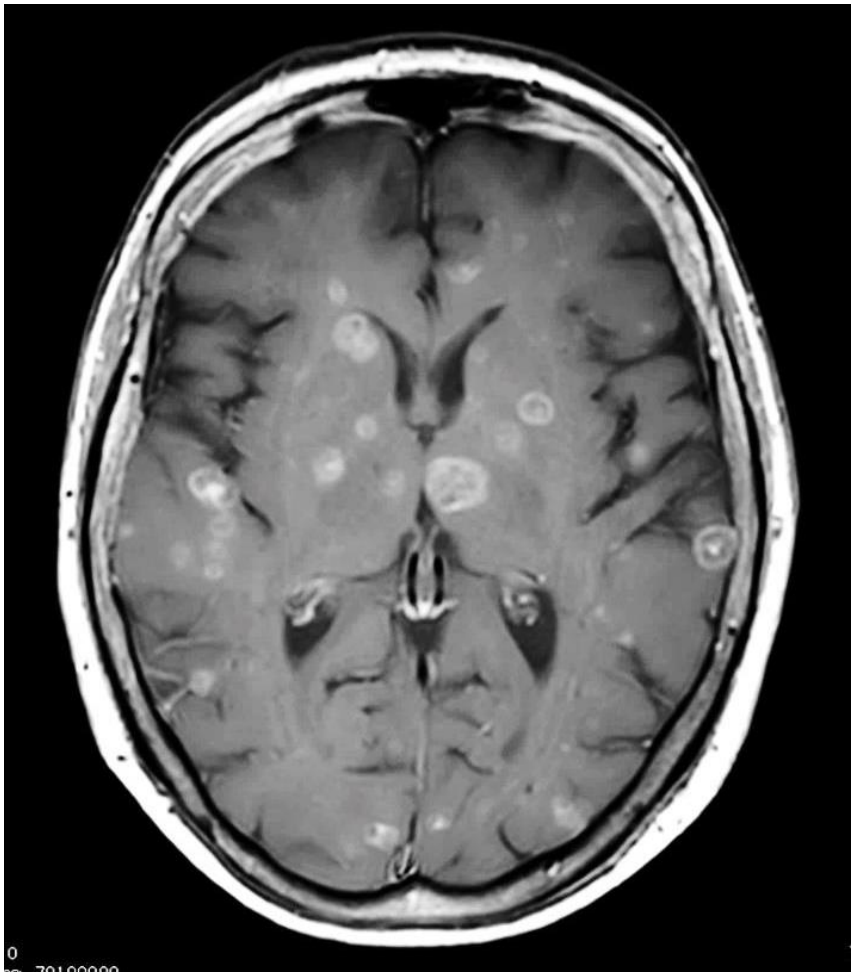
Frontiers in SRS for BM

- multiple BM (+ status in treatment guidelines)
- tumor bed SRS after surgery
- neoadjuvant SRS
- distinction between recurrence and therapy induced changes

SRS for multiple brain metastases

Cases





National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Limited Brain Metastases

NCCN Guidelines Index
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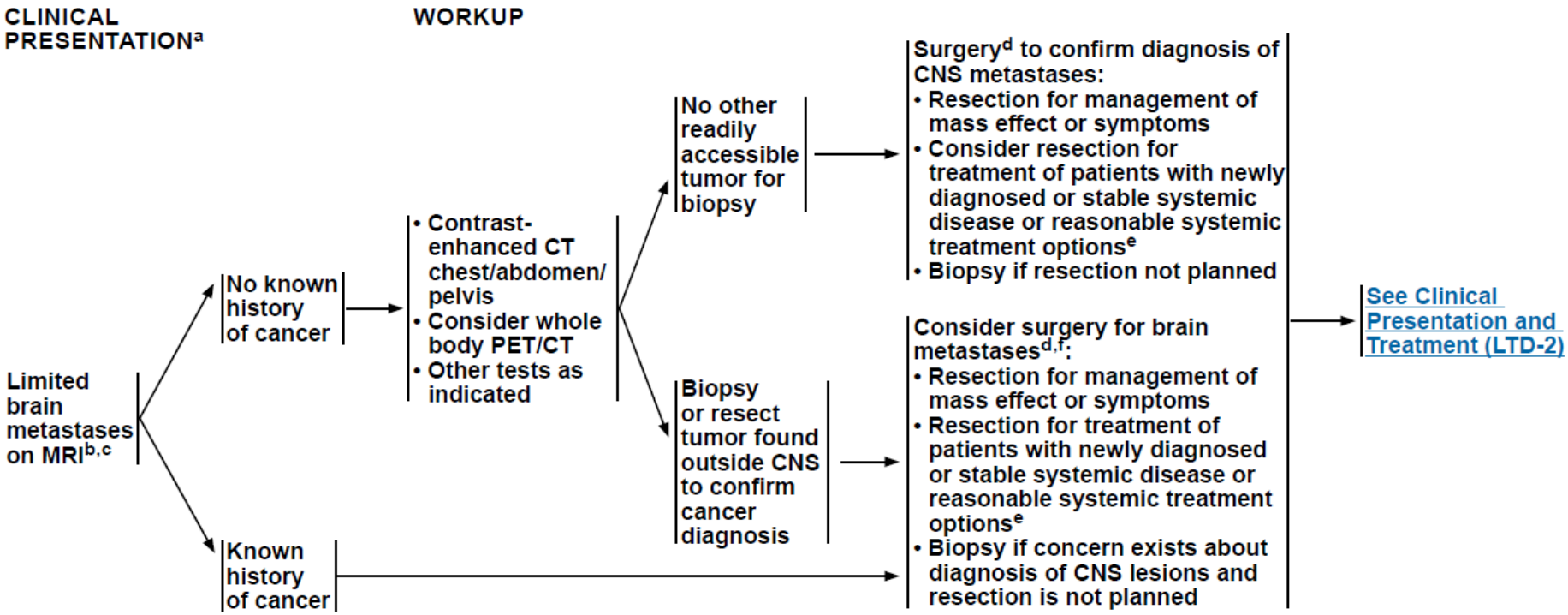
Discussion



[a] See 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-E).

[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, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. Lancet Oncol 2014;15:387-395.)

[d] See Principles of Brain Tumor Surgery (BRAIN-B).

[e] For secondary CNS lymphoma treatment may include systemic treatment, whole-brain or focal RT, or 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, Morris DE, Carey LA, Ladha AM, Brem S: Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. J Natl Compr Cancer Netw 2008; 6:505-513.)

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

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Neuro-Oncology
19(2), 162–174, 2017 | doi:10.1093/neuonc/now241

Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO)

Table 3 Recommendations regarding treatment of newly diagnosed brain metastases

- Surgical resection should be considered in patients with a limited number (1 to 3) of newly diagnosed brain metastases, especially in case of lesions of ≥3 cm in diameter (symptomatic or not), lesions with necrotic or cystic appearance and edema/mass effect, lesions located in the posterior fossa with associated hydrocephalus, and lesions located in symptomatic eloquent areas (Good Practice Point).
- Surgical resection is recommended when the systemic disease is absent/controlled and the KPS is 60 or more, as it can prolong survival (level A).
- Surgical resection can be an option when the systemic disease is active but effective systemic treatment options are available or when the primary tumor is relatively radioresistant (ie, melanoma, renal carcinoma, colon carcinoma) (Good Practice Point).
- Stereotactic radiosurgery should be considered in patients with metastases of a diameter of ≤3–3.5 cm (level B).
- Stereotactic fractionated radiotherapy (SFRT) should be considered in patients with metastases larger than 3 cm in maximum diameter and a larger irradiation volume than 10 or 12 cm^3 due to increased toxicity and radiation necrosis of normal brain tissue (Good Practice Point).
- Stereotactic radiosurgery and/or stereotactic fractionated radiotherapy should be considered in patients with metastases that are not resectable due to location (ie, basal ganglia, brain stem, eloquent cortical areas) or with comorbidities precluding surgery (ie, older age, cardiovascular disease, etc) (Level C).
- When both surgical resection and SRS/SFRT are feasible, the choice should be made on a case-by-case basis with consideration given to tumor size, site, type of neurological symptoms, need for steroids, patient preference, and/or physician expertise (Good Practice Point).
- Following complete surgical resection or SRS for a limited number of brain metastases, adjuvant WBRT is not unequivocally recommended due to lack of a survival advantage and risk of neurocognitive dysfunctions (level A).
- When withholding adjuvant WBRT following complete surgical resection or SRS, a close monitoring with MRI (every 3–4 mo) is recommended (Good Practice Point).
- When withholding adjuvant WBRT after surgical resection of brain metastases, postoperative stereotactic radiosurgery or stereotactic fractionated radiotherapy to the resection cavity should be given to maintain and increase local control (level C). As the post-resection cavity volume is usually smaller than pre-resection metastasis volume, it is recommended to perform a postoperative dedicated brain MRI for the SRS/SFRT, while the timing appears not to be relevant (Good Practice Point).
- When employing initial WBRT, a monitoring of cognitive functions with specific batteries is recommended (Good Practice Point).
- The decision regarding whether to employ SRS, SFRT, WBRT, alone or in combination, for patients with multiple brain metastases comes down to clinical discretion, patient preference and logistical considerations with the absolute number of brain metastases becoming less crucial (Good Practice Point).
- WBRT or best supportive care should be considered for patients with short life expectancy (low KPS score and/or progressive systemic disease) (level B).

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Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study

Lancet Oncol 2014; 15: 387–95

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phase 2 trail (evidence level IIIa)

- pat. with newly diagnosed 1-10 BM
- defined MR imaging protocol
- max. volume: 10 ml for largest and 15 ml total
- excluded: KPS<70; leptomeningeal dissemination; sarcoma/lymphoma
- **primary endpoint:** overall survival
- **secondary endpoints:** neurological death, worsening neurological status local recurrence, distant failure, leukoencephalopathy, salvage therapies

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- 1194 pat, 23 centres, 2009-2012

No. of lesions per Patient	singular	2-4	5-10
Patient No.	455	531	208
Median OS (months)	13.9	10.8	10.8
Adverse Events	2%	2%	3%

- primary and secondary endpoints did not differ significantly between groups of 2-4 vs. 5-10 BM

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Conclusion:

- SRS without WBRT is not inferior in 2-4 vs. 5-10 BM
- SRS has fewer side-effects than WBRT
- => suitable for patients with ≤ 10 brain mets

SRS for Multiple Brain Metastases: Prognostic Factors

Overall survival influenced by:

- KPS, age, RPA, primary disease control, male, lung cancer, HER 2 neg. leptomeningeal seeding, SCLC, melanomatous tumor, use of TKI/ mTOR/ VEGF inhibitors
- total treatment volume
- volume of largest metastasis
- symptomatic recurrence and presents of initial neuro symptoms
- marginal dose
- > 1 brain met

Amendola 2002, Baschnagel 2013, Bhathnagar 2006, Caballo 2011, Chang 2010, Choi 2013, Cochran 2012, Gonda 2014 a,b, Grandhi 2012, Hunter 2012, Jang 2016, Jawahar 2005, Karlsson 2009, Kim 2008, Knoll 2016, Kuremsky 2013, Kurtz 2014, Lam 2014, Liew 2011, Likhacheva 2013, Maranzano 2012, Matsunaga 2010, Mininiti 2013, Mohammadi 2012, Nam 2005, Rava 2013, Radlow 2013, Salvetti 2013, Serizawa 2000, 2010, Suzuki 2000, Vern-Gross 2012, 2014, Tam 2014, Yamamoto 2012, 2013, Yomo 2013, Zhang 2017

Current prospective trails *(registered at ClinicalTrials.gov)*

Table 1. Currently ongoing clinical trials investigating the role of radiosurgery for multiple brain metastases

Trial	PI	Number of patients	Standard arm	Experimental arm	Number of brain metastases
NCT02353000	Jaap Zindler (MAASTRO Clinic, The Netherlands)	260 estimated	WBRT	SRS	4–10
NCT01592968	Jing Li M.D. Anderson Cancer Center	100 estimated	WBRT	SRS	4–15
NCT03075072	Ayal Aizer Brigham and Women's Hospital	196 estimated	WBRT	SRS	5–20
NAGKC 12–01, NCT01731704	Igor J Barani University of California, San Francisco	120 estimated	WBRT	SRS (Gamma Knife)	≥ 5

from Kraft et al. 2019

Post OP SRS for brain metastases

Clinical Investigation: Central Nervous System Cancer

International Journal of Radiation Oncology biology • physics

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A Phase 2 Trial of Stereotactic Radiosurgery Boost After Surgical Resection for Brain Metastases

Cameron Brennan, MD,*,†,£ T. Jonathan Yang, MD,‡,£ Patrick Hilden, MS,§ Zhigang Zhang, PhD,§ Kelvin Chan, RT(T),‡ Yoshiya Yamada, MD,‡ Timothy A. Chan, MD, PhD,*,‡ Stella C. Lymberis, MD,# Ashwatha Narayana, MD,** Viviane Tabar, MD,† Philip H. Gutin, MD,† Åse Ballangrud, PhD,‖ Eric Lis, MD,¶ and Kathryn Beal, MD‡

*Human Oncology and Pathogenesis Program, †Department of Neurosurgery, ‡Department of Radiation Oncology, §Department of Epidemiology and Biostatistics, ‖Department of Medical Physics, and ¶Department of Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York; #Department of Radiation Oncology, New York University Langone Medical Center, New York, New York; and **Department of Radiation Oncology, Greenwich Hospital, Greenwich, Connecticut.

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phase 2 trail *(2004 – 2009)*

- median FU 12 months
- 49 patients / 50 lesions;
- 18 Gy *(median; 15-22 Gy)*

results:

- 39 patients with 40 lesions received SRS
- local failure 22%; distant failure 44% *(after 12 month)*
- SRS reduced local failure significantly *(P = 0.008)*

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- significant prognostic factors for local control:
  - NSCLC histology *(P = 0.048)*
  - tumor diameter < 3 cm *(P = 0.01)*
  - deep localization *(P = 0.036)*
- high risk for local failure:
  - superficial (dural/pial)
  - tumor ≥3 cm *(53.3 % after 12 month)*
- significant risk of distant failure in infra- vs. supra-tentorial tumors (P<0.001)

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

in press

Post-operative stereotactic radiosurgery following excision of brain metastases: A systematic review and meta-analysis

Zarique Z. Akanda [a], Wei Hong [b], Sofia Nahavandi [c], Neda Haghighi [d], Claire Phillips [d], David L. Kok [d,e,*]

[a] Eastern Health; [b] Department of Medical Oncology, St Vincent's Hospital; [c] Austin Health; [d] Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne; and [e] Department of Clinical Pathology, The University of Melbourne, Parkville, Australia

Meta-analysis:

- 50 studies with 3458 patients
- parameters: - local control after 12 month (LC12)
  - presents of radiation necrosis
  - leptomeningeal disease dissemination

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results:

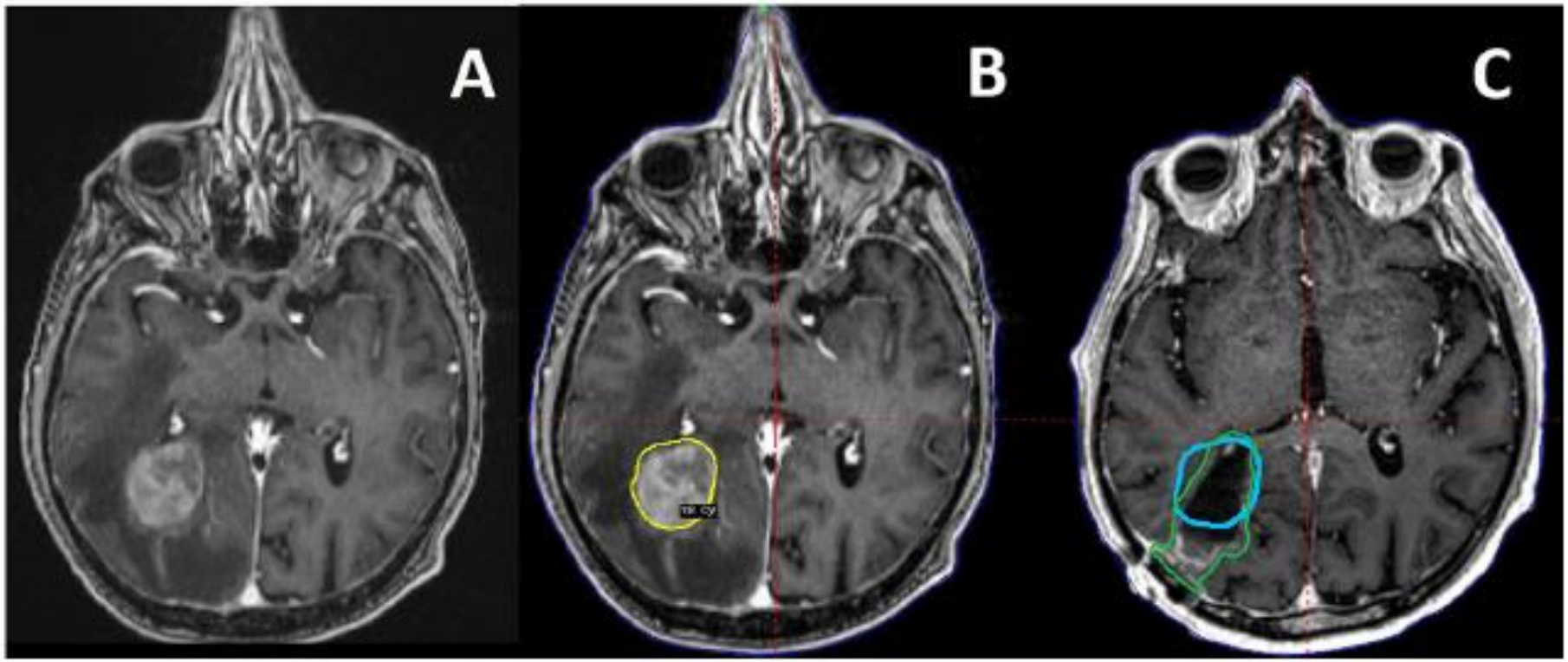
- overall LC12 83.7%
- SRS fractionated better than single fraction *(LC12 87.3% vs. 80.0%; p=0.021)*
- no benefit of adding a margin *(LC12 84.3% vs. 83.1%; ns.)*
- 6.9% radiation necrosis; 13% leptomeningeal disease

conclusion:

- post-op SRS to the resection cavity as a safe and efficacious
- fractionated SRS appears to be beneficial

Neoadjuvant SRS for brain metastases

Case *(by Routman et al.2018)*



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Preoperative stereotactic radiosurgery before planned resection of brain metastases: updated analysis of efficacy and toxicity of a novel treatment paradigm

Roshan S. Prabhu, MD, MS,[1,2] Katherine R. Miller, BS,[1] Anthony L. Asher, MD,[1,3] John H. Heinzerling, MD,[1,2] Benjamin J. Moeller, MD, PhD,[1,2] Scott P. Lankford, MD,[1,2] Robert J. McCammon, MD,[1,2] Carolina E. Fasola, MD, MPH,[1,2] Kirtesh R. Patel, MD,[4] Robert H. Press, MD,[5] Ashley L. Sumrall, MD,[1] Matthew C. Ward, MD,[1,2] and Stuart H. Burri, MD[1,2]

[1]Levine Cancer Institute, Atrium Health; [2]Southeast Radiation Oncology Group; and [3]Carolina Neurosurgical and Spine Associates, Charlotte, North Carolina; [4]Department of Therapeutic Radiology, Yale University School of Medicine, New Haven, Connecticut; and [5]Department of Radiation Oncology, Emory University and Winship Cancer Institute, Atlanta, Georgia

J Neurosurg. 2018

retrospective analysis *(2005-2016)*

- 117 patients with 125 BM
- single fraction SRS 15 Gy *(median)*
- median time from SRS to surgery: 2 days
- tumor volume 8.3 cm^3 *(median)*

results: after 1 and 2 years

- local control rates: 80.1% / 74.9%
- leptomeningeal disease rates: 4.3%
- symptomatic radionecrosis rates: 2.6% and 4.8%
- overall grade 3 toxicity: 2.6%

NEUROSURGERY RESEARCH—HUMAN—CLINICAL STUDIES

Comparing Preoperative With Postoperative Stereotactic Radiosurgery for Resectable Brain Metastases: A Multi-institutional Analysis

*Department of Radiation Oncology and Winship Cancer Institute, Emory University, Atlanta, Georgia; ‡Southeast Radiation Oncology Group, Levine Cancer Institute, Carolinas Healthcare System, Charlotte, North Carolina; §Carolina Neurosurgery and Spine Associates, Levine Cancer Institute, Charlotte, North Carolina; ¶Biostatistics and Bioinformatics Shared Resource, Winship Cancer Institute, Emory University, Atlanta, Georgia; ||Department of Neurological Surgery, Emory University, Atlanta, Georgia

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Scott D. Wait, MD§
Walter J. Curran, MD*
Hui-Kuo G. Shu, MD, PhD*
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retrospective multi-centre analysis *(2005-2013)*

- pre OP vs. post OP SRS
- main parameters:
  - overall survival
  - local and distant control
  - leptomeningeal disease
  - symptomatic radiation necrosis

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results:

- 180 patients with 189 BM: 66 pre OP vs. 116 post-OP SRS
- no difference for overall survival, local and distant recurrence
- leptomeningeal disease at 2 years:

  pre OP vs. post OP SRS = 3.2% vs 16.6% *(p = 0.010)*
- symptomatic radiation necrosis at 2 years:

  pre OP vs. post OP SRS = 4.9% vs 16.4% *(p = 0.010)*

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conclusion:

“preoperative SRS for resectable BM can provide similar outcomes compared with postoperative SRS and may have important advantages regarding leptomeningeal disease and radionecrosis.”

→ need for prospective data from well-designed trials to confirm this.

Current prospective trails *(registered at ClinicalTrials.gov)*

Trial Type	Sponsor	Patient Number	Primary Outcome Measure	Estimated Completion
Phase III **Randomized-Controlled Trial**	Mayo Clinic	140	CNS-CE event (up to 5 years)	2025
Phase II	University Health Network, Toronto	30	Symptomatic radiation toxicity rate (at 1 year)	2022
Phase I/II	Case Comprehensive Cancer Center	36	MTD at day 0, Local control rate (up to 1 year)	2019
Phase II	Indiana University	44	Local control rate (6 months)	2021
Phase I Dose Escalation	Cedars-Sinai Medical Center	25	MTD at 1- month	2020
Phase I **Dose Escalation vs. De-escalation 15 Gy vs. 12 Gy**	University of Alabama at Birmingham	20	MTD at 1 year	2018 (actual completion)

MTD= maximum tolerated dose, CNS-CE = Central Nervous System Composite Endpoint

Treatment induced changes vs. local recurrence

Neuro-Oncology Advance Access published July 28, 2016

Neuro-Oncology

Neuro-Oncology 2016; **0**, 1–8, doi:10.1093/neuonc/now149

Dynamic *O*-(2-^{18}F-fluoroethyl)-L-tyrosine positron emission tomography differentiates brain metastasis recurrence from radiation injury after radiotherapy

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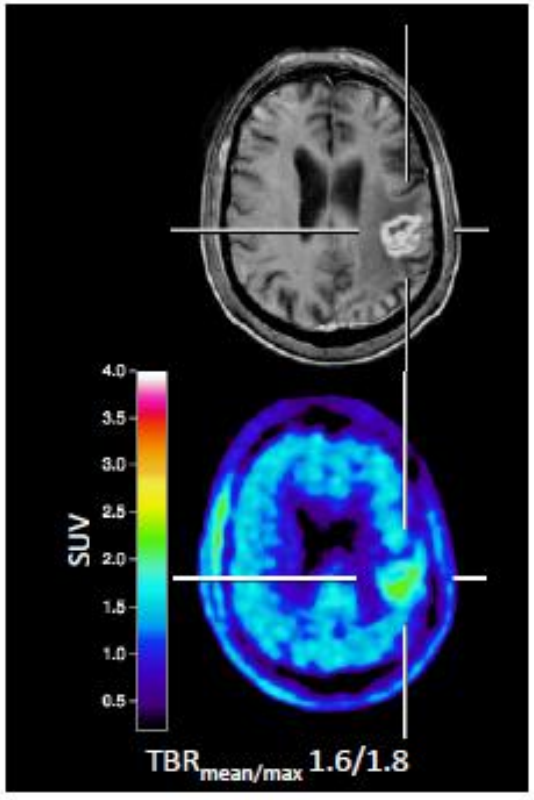
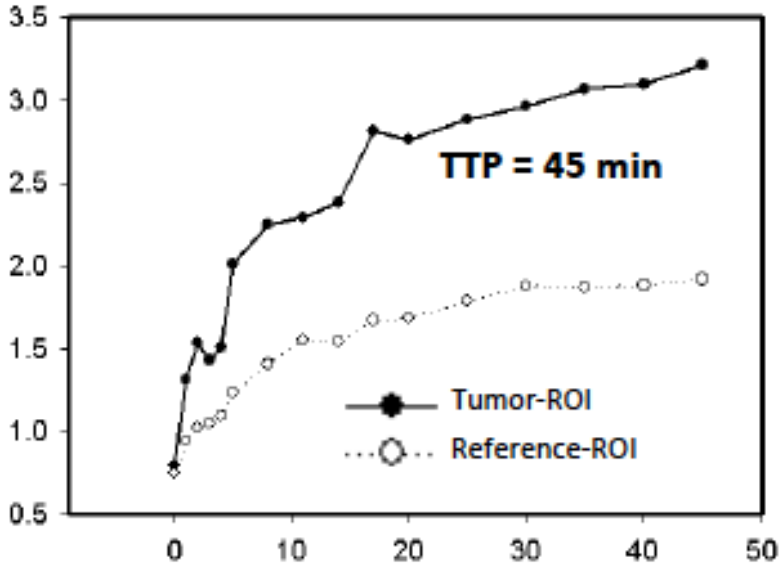


Radiation injury
(after RS of a breast cancer BM)



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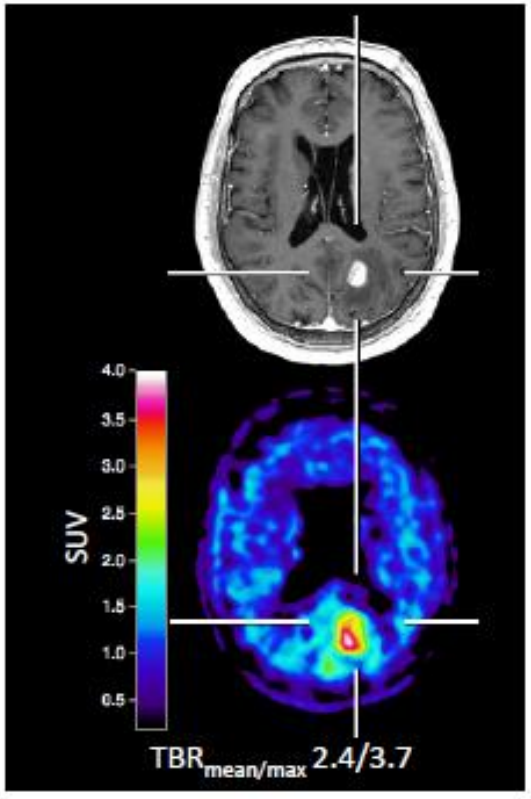
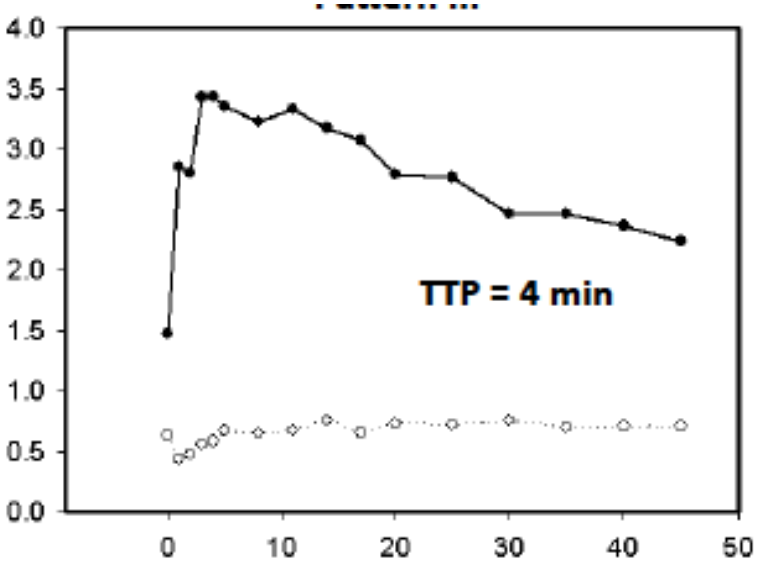


Recurrent metastasis
(after RS of a malignant melanoma BM)



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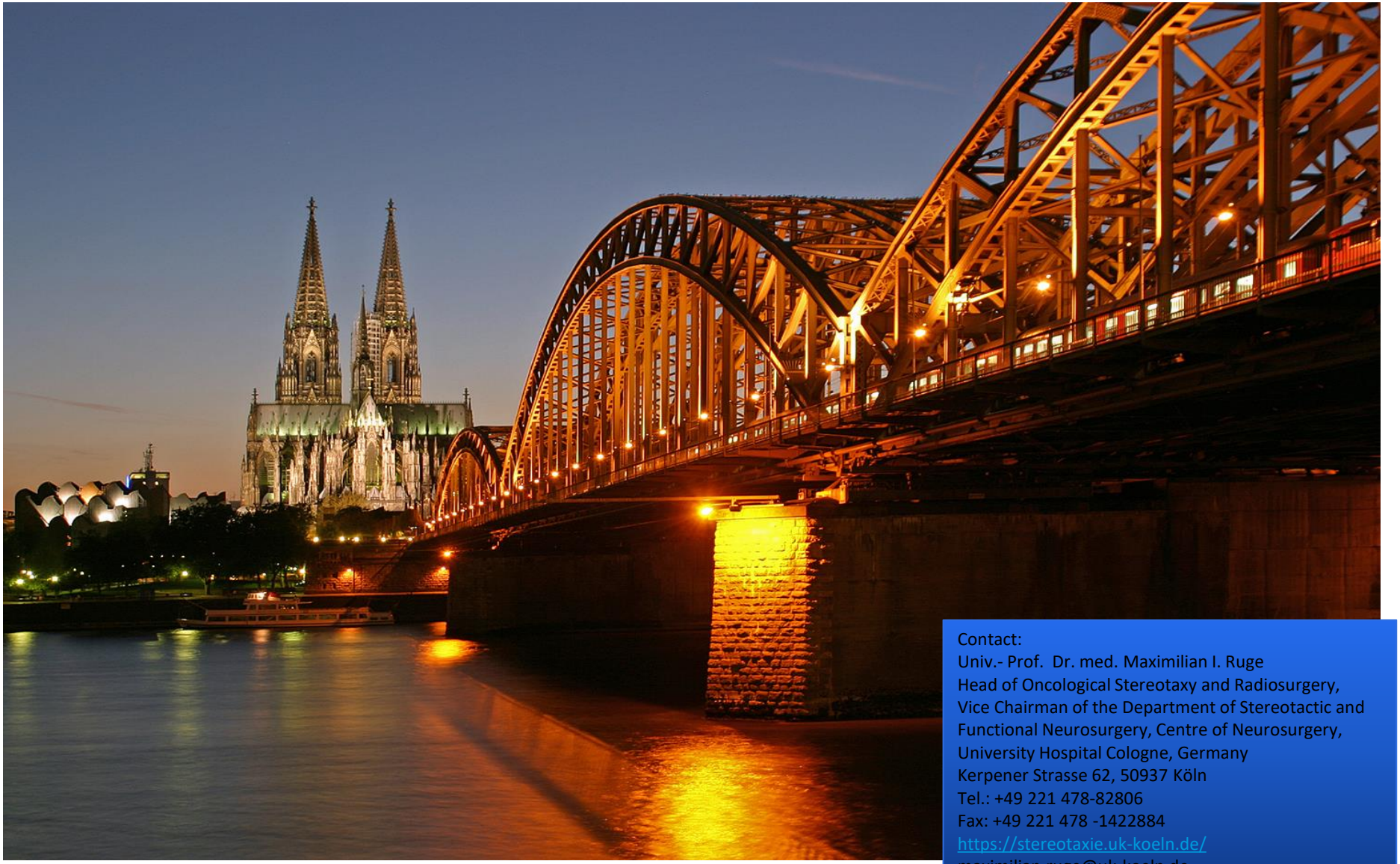

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Single vs. fractionated SRS for large brain metastases

Clinical Investigation

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Single versus Multifraction Stereotactic Radiosurgery for Large Brain Metastases: An International Meta-analysis of 24 Trials

Eric J. Lehrer, MD, MS,* Jennifer L. Peterson, MD,†,‡ Nicholas G. Zaorsky, MD,§ Paul D. Brown, MD,‖ Arjun Sahgal, MD,¶ Veronica L. Chiang, MD,# Samuel T. Chao, MD,** Jason P. Sheehan, MD, PhD,†† and Daniel M. Trifiletti, MD†,‡

Received May 11, 2018. Accepted for publication Oct 24, 2018.

Meta-analysis

- 24 studies with 1887 brain metastases (2008-2017)
- multi- vs. single fraction SRS
- parameters: - local control after 12 month (LC12)
  - presents of radiation necrosis
- group A: 4-14 cm^3 vs. group B: > 14 cm^3
- definitive vs. post OP treatment
- random effects estimate

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Received May 11, 2018. Accepted for publication Oct 24, 2018.

Results: LC12

definitive SRS:

- group A: single- / multi-fraction SRS: 77.6% vs. 92.9% *(P=0.18)*
- group B: single- / multi-fraction SRS: 77.1% vs. 79.2% *(P=0.76)*

post OP SRS:

- group B: single- / multi-fraction SRS: 62.4% vs. 85.7% *(P=0.13)*

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Received May 11, 2018. Accepted for publication Oct 24, 2018.

Results: radionecrosis

definitive SRS:

- group A: single- / multi-fraction SRS: 23.1% vs. 7.3% ***(P=0.003)***
- group B: single- / multi-fraction SRS: 11.7% vs. 6.5% *(P=0.29)*

post OP SRS:

- group B: single- / multi-fraction SRS: 7.3% vs. 7.5% *(P=0.13)*

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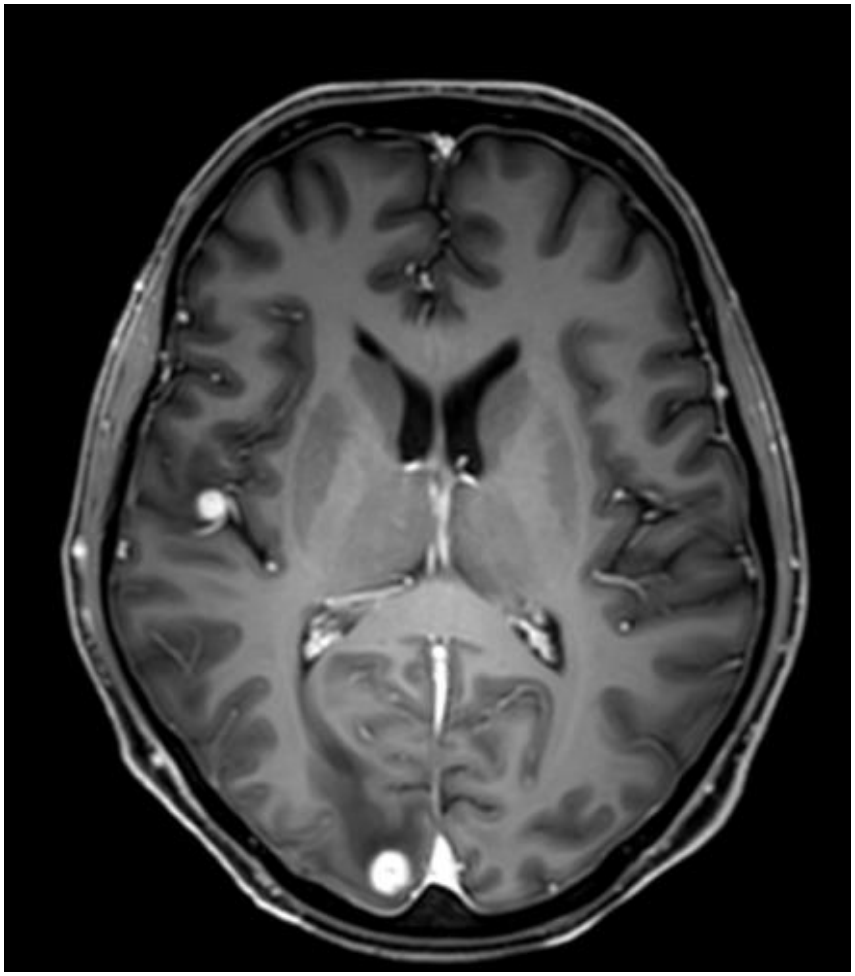
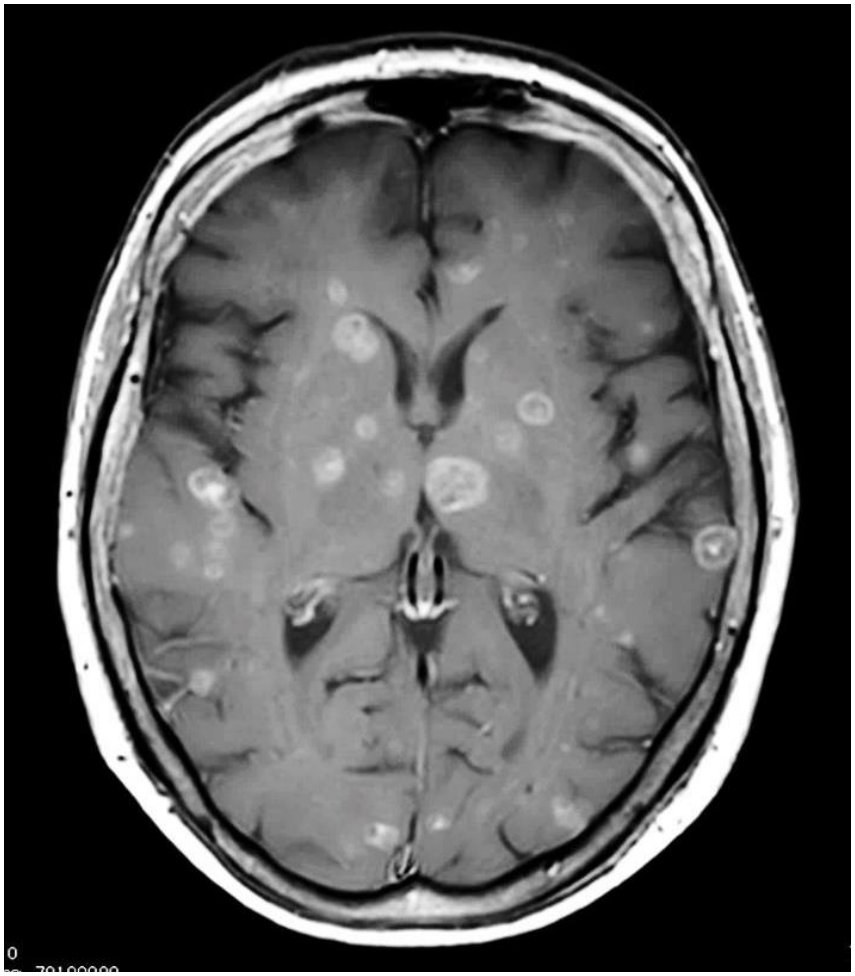
Conclusion:

"treatment for large brain metastases with MF-SRS regimens may offer a relative reduction of radionecrosis while maintaining or improving relative rates of 1-year LC compared with SF-SRS. These findings are hypothesis-generating and require validation by ongoing and planned prospective clinical trials."

Cases





SRS for 1-10 Brain Metastases: Facts

- evidence level IIIa - IV
- number of BM treated has no effect on overall survival
- overall treatment volume to be considered
- high rate of salvage therapies
- close follow-up when SRS alone
- median OS 7-13 months *

Yamamoto, 2014, Serizawa, 2000, 2010, *Chang, 2010, Park 2009, and other Authors

SRS for > 10 Brain Metastases: Facts

- evidence level III - IV
- no significant difference in OS regarding number of lesions but overall treated tumor volume *
- no significant difference in OS between patients with 1-5 vs. 6-10 vs. 11-15
- vs. >15 BM **
- higher risk for new distant brain metastases with increased number of treated lesions (<14 vs. >14 mets*** , <15 vs. >15 mets**)

=> SRS can be an effective and feasible option in selected patients with >10 brain lesions

* Serizawa et al. 2000, Grandhi et al. 2012, Bhatnagar et al. 2006, Yamamoto et al. 2013, ** Chang et a. 2010,
***Grandhi et al. 2012

SRS for Multiple Brain Metastases: Perspective

Pending Results: SRS vs. WBRT for Multiple Brain Mets:

- **NCT01731704 trial** *(by North American Gamma Knife Consortium)*
  - ≥ 5 brain mets (KPS ≥70) SRS vs. WBRT (30 Gy in 10 fractions)
  - primary end point: cognitive function after 6 mo.
  - sec. endpoints: cognitive function after 12 mo., quality of life, salvage treatment and OS
- **NCT01644591 / NCT01592968** *(by MD Anderson Cancer Center)*
  - 4-10 brain mets SRS vs. WBRT
  - neurocognitive outcome in melanoma / non melanoma patients
- and many other RCT trails registered at *clinicaltrails.gov*