Management of Brain Metastases: Whole Brain Radiotherapy vs. Stereotactic Radiosurgery

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Current trials.

- Drug trials \( n = 40 \)
- Combination therapy (RT + chemo / targeted therapy) \( n = 10 \)
- Resection and radiotherapy/radiosurgery (pre- or postoperative) \( n = 5 \)
- Radiosurgery for multiple brain metastases \( n = 6 \)
- Advanced RT techniques (IMRT, integrated boost, hippocampal sparing) \( n = 9 \)
Background.
Background.

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial

Dr Eric L Chang, Jeffrey S Wefel, Kenneth R Hess, Pamela K Allen, Frederick F Lang, David G Kornguth, Rebecca B Arbuckle, J Michael Swint, Almon S Shiu, Moshe H Maor, Christina A Meyers


“Patients treated with SRS plus WBRT were at a greater risk of a significant decline in learning and memory function by 4 months compared with the group that received SRS alone.”
Background.

Neurocognitive Function of Patients with Brain Metastasis Who Received Either Whole Brain Radiotherapy Plus Stereotactic Radiosurgery or Radiosurgery Alone

Hidefumi Aoyama, Masao Tago, Norio Kato, Tatsuya Toyoda, Masahiro Kenjyo, Saeko Hirota, Hiroki Shioura, Taisuke Inomata, Etsuo Kunieda, Kazushige Hayakawa, Keiichi Nakagawa, Gen Kobashi, Hiroki Shirato


“For most brain metastatic patients, control of the brain tumor is the most important factor for stabilizing neurocognitive function”
IMRT – hippocampal sparing.

Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial.


J Clin Oncol. 2014 Dec 1;32(34):3810-6

„Mean relative decline in HVLT-R from baseline to 4 months was 7.0% vs. 30% in the historical control (P.001).”
HIPPORAD trial.

Whole-brain irradiation with hippocampal sparing and dose escalation on metastases: neurocognitive testing and biological imaging.

Prospective randomized multi-center trial

Initiating Center: University Medical Center Freiburg

Primary endpoint:
- neurocognitive function 3 months from RT
- verbal learning and memory test compared to baseline
SRS of multiple brain metastases.


Masaaki Yamamoto, Toru Serizawa, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Mitsuya Sato, Tomohide Akimitsu, Kenji Kubo


- 1194 patients / 1-10 brain metastases
- Gamma-Knife SRS (20-22 Gy margin dose)
- Overall after SRS non-inferior for patients with 5-10 brain metastases vs. patients with 2-4 brain metastases
- No significant difference regarding treatment-related toxicity
- Conclusion: SRS is a valid treatment alternative to WBRT for 5-10 brain metastases
Salvage therapy.


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- Regular follow-up MRI and salvage therapy for 49% of patients
- 77% of salvage therapies by repeated SRS
Salvage therapy.

Stereotactic radiosurgery for patients with multiple brain metastases. A multimodal institutional perspective.

Masaaki Yamamoto, Toru Serizawa, Takashi Shuto, Atsuya Akabane, Yoshinori Higuchi, Jun Kawagishi, Kazuhiro Yamanaka, Yasunori Sato, Hidefumi Jokura, Shoji Yomo, Osamu Nagano, Hiroyuki Kenai, Akihito Moriki, Satoshi Suzuki, Yoshihisa Kida, Yoshiyasu Iwai, Motohiro Hayashi, Hiroaki Onishi, Masazumi Gondo, Tomohide Akimitsu, Kenji Kubo


1. Clinical benefit from more sensitive imaging?

2. Clinical benefit from early repeated SRS for new brain metastases?
CYBER-SPACE

CyberKnife radiosurgery for patients with brain metastases diagnosed with either SPACE or MPRAGE sequence – A prospective randomized evaluation of response and toxicity

Clinical Phase: Phase II
Principal Investigator: Prof. Dr. Dr. Jürgen Debus
PD Dr. med. Stefan Rieken
Study coordinator: Dr. med. Rami El Shafie
SPACE vs. MPRAGE.

Usefulness of contrast-enhanced T1-weighted sampling perfection with application-optimized contrasts by using different flip angle evolutions in detection of small brain metastasis at 3T MR imaging: comparison with magnetization-prepared rapid acquisition of gradient echo imaging.

Inclusion Criteria
- Cerebral oligometastases confirmed by MRI (not resected, maximum number of 10)
- Primary malignant illness not SCLC
- Age ≥ 18 years of age
- KPI ≥ 70%

Primary Endpoint:
Ineligibility for further SRS at 12 months after initial treatment

Secondary Endpoints:
- OS at 12 months after initial SRS
- Cognitive function and quality of life at 6 months after initial SRS
- Toxicity

Duration:
- Recruitment: 24 months
- Follow-up: 12 months
Adjuvant Radiotherapy.

Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study.

Martin Kocher, Riccardo Soffietti, Ufuk Abacioglu, Salvador Villà, Francois Fauchon, Brigitta G. Baumert, Laura Fariselli, Tzahala Tzuk-Shina, Rolf-Dieter Kortmann, Christian Carrie, Mohamed Ben Hassel, Mauri Kouri, Egils Valeinis, Dirk van den Berge, Sandra Collette, Laurence Collette, and Rolf-Peter Mueller

J Clin Oncol. 2011 Jan 10;29(2):134-41

Adjuvant radiotherapy significantly reduces the risk of local relapse after neurosurgical resection of cerebral metastases.
The role of stereotactic RT.

- Evidence for postoperative SRS/FSRT of the resection cavity after neurosurgical resection of brain metastases:

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Treatment Details</th>
<th>LC (1 year)</th>
<th>LC (2 years)</th>
<th>LRC (1 year)</th>
<th>LRC (2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minniti et al., Int. J. Radiat. Oncol. Biol. Phys., 2013</td>
<td>101</td>
<td>margin = 2 mm, 3 x 9 Gy FSRT (linac)</td>
<td>93%</td>
<td>84%</td>
<td>50%</td>
<td>46%</td>
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<tr>
<td>Connolly et al., Neuro-oncology, 2013</td>
<td>33</td>
<td>15 x 2.67 Gy 3DCRT (linac)</td>
<td>90%</td>
<td>86%</td>
<td>61%</td>
<td>51%</td>
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<tr>
<td>Jensen et al., Journal of neurosurgery, 2011</td>
<td>112</td>
<td>17 Gy @ 50% isodose (SRS), SRS of all additional lesions</td>
<td>80%</td>
<td></td>
<td>35%</td>
<td>Median LRC = 6,9 months</td>
</tr>
<tr>
<td>Specht et al., Stahlentherapie und Onkologie, 2016</td>
<td>46</td>
<td>7 x 5 Gy @ 95-100% isodose (FSRT)</td>
<td>88%</td>
<td></td>
<td>48%</td>
<td>median OS = 25 months</td>
</tr>
</tbody>
</table>
SRS of the resection cavity.

Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial.

Anita Mahajan, Salmaan Ahmed, Mary Frances McAleer, Jeffrey S Weinberg, Jing Li, Paul Brown, Stephen Settle, Sujit S Prabhu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Sulman, Ian E McCutcheon, Syed Azeem, Daniel Cahill, Claudio Tatsui, Amy B Heimberger, Sherise Ferguson, Amol Ghia, Franco Demonte, Shaa Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R Hess, Dr Ganesh Rao


- Improved local control for SRS of resection cavity vs. observation
SRS of the resection cavity.

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• Improved local control for SRS of resection cavity vs. observation

• Less neurocognitive toxicity by SRS compared to WBRT

BUT …

• Significantly inferior local control for cavity SRS compared to WBRT
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unresected metastases

incomplete resection

radiation dose

MR imaging

cavity size

margins

fractionation

unresected metastases

incomplete resection

radiation dose

MR imaging

cavity size

margins

fractionation

unresected metastases

incomplete resection

radiation dose

MR imaging

cavity size

margins

fractionation
ESTRON

Evaluation of Stereotactic Radiotherapy of the Resection Cavity after Surgery of Brain metastases compared to post-operative whole-brain radiotherapy

Clinical Phase: Phase II
Principal Investigator: Prof. Dr. Dr. Jürgen Debus
PD Dr. med. Stefan Rieken
Study coordinator: Dr. med. Rami El Shafie
Inclusion Criteria
- MRI confirmed cerebral metastases
- Neurosurgical resection of one cerebral metastasis
- age ≥ 18 years of age
- Karnofsky Performance Score ≥ 60

Primary Endpoint:
Neurological progression-free survival (nPFS)

Secondary Endpoints:
- Time to local and loco-regional recurrence
- OS
- Quality of life (QLQ-C30 and BN20)
- Neurocognition

Duration:
- Recruitment: 24 months
- Follow-up: 12 months

Total 50 patients:
Screen patients for inclusion and exclusion criteria, obtain informed consent.
Collect trial relevant data and patient history.

**A**
- SRS of resection cavity (n=25)
  - 7 x 5 Gy to surrounding 70%-isodose
- SRS of all unresected lesions
  - 20 Gy @ 70%-isodose
  - 18 Gy @ 70%-isodose or multisession FSRT (depending on size)

Clinical assessment, neuroimaging after therapy completion and thereafter every 3 months

**B**
- WBRT (n=25)
  - 30 Gy in 10 Fx
  - Treatment planning & Application of treatment

Clinical assessment, neuroimaging after therapy completion and thereafter every 3 months

final study
Summary – Future perspectives.

• Increased use of **stereotactic RT instead of WBRT** due to advances in precision techniques and the rationale of reducing toxicity

• **Resection cavity**: „All has not been said!“ – Despite current and prospective evidence

• Reduction of **integral dose** to healthy brain vs. **tumor control**?

• Potential of **OAR-sparing intensity-modulated WBRT** (e.g. hippocampal sparing)
Thank you for your attention!