Symposium Oligo-metastasis Zurich 2016

Stereotactic Radiosurgery for the Management of 5 or more Brain Metastases: New options to accept the challenge

Brain Metastases: Clinical Endpoints

- Local control
- Brain tumor control
- Regional control: Freedom from new brain metastases
- Quality of Life
  - Neurocognition
- Extracranial disease control
- Survival
Brain Metastases: Introduction

Brain Metastases: Epidemiology of Brain Metastases

<table>
<thead>
<tr>
<th>Primary Tumor</th>
<th>Relative Prevalence of Brain Metastases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon: 5%</td>
<td>Annual U.S. incidence: &gt; 170K</td>
</tr>
<tr>
<td>Melanoma: 9%</td>
<td>Ratio Mets/Primary: 16:1</td>
</tr>
<tr>
<td>Unknown primary: 11%</td>
<td>All Cancer Patients: 15 - 30%</td>
</tr>
<tr>
<td>Other known primary: 13%</td>
<td>Autopsy incidence: 10 - 30%</td>
</tr>
<tr>
<td>Breast: 15%</td>
<td>Mean age: 60 years</td>
</tr>
<tr>
<td>Lung: 48%</td>
<td>Median survival: 4-6 months</td>
</tr>
</tbody>
</table>

*Incidence increasing with better systemic Rx and improved survival

Gaspar et al. IJROBP 1997; 37: 745-751

Prognostic Scoring Systems

Stratification of cancer patients with brain metastases

RPA classes I - III

<table>
<thead>
<tr>
<th>KPS≥70 Age&lt;65 and Controlled primary site and No mets outside CNS</th>
<th>Median OS 7.1 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS ≥ 70 Primary site active and/or Mets outside CNS present Age ≥ 65</td>
<td>4.2 months</td>
</tr>
<tr>
<td>KPS&lt; 70</td>
<td>2.3 months</td>
</tr>
</tbody>
</table>

Gaspar et al. IJROBP 1997; 37: 745-751
Stratification of cancer patients with brain metastases: GPA Score

Non-small cell and small cell lung cancer

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0 20 40 60 80</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>0 20 40 60 80</td>
<td>0 1 2 3 4 5</td>
</tr>
<tr>
<td>No of BM</td>
<td>0 20 40 60 80</td>
<td>0 1 2 3 4 5</td>
</tr>
</tbody>
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Median survival (in months) by GPA: 8.1, 3.6, 1.5, 2.2, 1, 0.2, 0.05, 0.01

Melanoma

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Median survival (in months) by GPA: 8.1, 3.6, 1.5, 2.2, 1, 0.2, 0.05, 0.01

Renal cell carcinoma

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
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Median survival (in months) by GPA: 8.1, 3.6, 1.5, 2.2, 1, 0.2, 0.05, 0.01

Colorectal cancer

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
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Median survival (in months) by GPA: 8.1, 3.6, 1.5, 2.2, 1, 0.2, 0.05, 0.01

Sperduto et al. JCO 2012; 30: 419-425

Brain Metastases: Treatment options

- Whole Brain Radiation Therapy (WBRT)
- Surgery +/- WBRT
- Surgery +/- localized radiation
- WBRT + Targeted Therapy
- WBRT + Chemotherapy
- **Stereotactic radiosurgery (SRS) +/- WBRT**
  - Chemotherapy
  - Surgery
  - Best Supportive Care

RS for the Management of 1-4 Brain Metastases

5 or more Brain Metastases
**Randomized Trials: SRS and WBRT**

Soliman H et al. Oncotarget 2016

<table>
<thead>
<tr>
<th>Nr. 7</th>
<th>RandomizedTrials: SRS and WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KEY</strong></td>
<td><strong>Patients included</strong></td>
</tr>
<tr>
<td>Rx-1</td>
<td>Kondziolka et al. RTOG 90-05 vs WBRT (Rx-14)</td>
</tr>
<tr>
<td>Rx-2</td>
<td>Andrews et al. RTOG 90-05 vs SRS (Rx-15)</td>
</tr>
<tr>
<td>Rx-3</td>
<td>Aoyama et al. JSROG93-01, SRS vs WBRT/SRS (5%)</td>
</tr>
<tr>
<td>Rx-4</td>
<td>Chang et al. RTOG 90-05 vs SRS (Rx-14)</td>
</tr>
<tr>
<td>Rx-5</td>
<td>Kocher et al. ESTRO 2002, SRS vs WBRT (Rx-15)</td>
</tr>
<tr>
<td>Rx-6</td>
<td>Brown et al. NCT02153779 (MetaSRS vs SRS) (Rx-15)</td>
</tr>
</tbody>
</table>

**Radiosurgical Dose Prescription?**

<table>
<thead>
<tr>
<th>Nr. 8</th>
<th>Radiosurgical Dose Prescription</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Dose Prescription</strong></td>
</tr>
<tr>
<td>Andrews et al. 2004</td>
<td>RTOG 90-05</td>
</tr>
<tr>
<td>Aoyama et al. 2006</td>
<td>18 – 25 Gy</td>
</tr>
<tr>
<td>Kocher et al. 2011</td>
<td>20 – 25 Gy</td>
</tr>
<tr>
<td>Brown et al. 2016</td>
<td>20 – 24 Gy</td>
</tr>
</tbody>
</table>

*We assigned radiosurgery doses in accordance with prescriptions from an earlier dose-escalation RTOG radiosurgery trial (90-05).* We treated metastases up to 2–2 cm in broadest diameter with a surface isodose prescription of 24–9 Gy, metastases larger than 2 cm but equal to or smaller than 3 cm with 18– Gy, and metastases larger than 3 cm and less than or equal to 4 cm.

**Radiosurgery** Both brain metastases and gross lesion diameter were allowed. The planning target volume consisted of the gross tumor volumes of all target metastases. A dose of 25 Gy was prescribed to the center of each metastases. The minimum dose at the surface of each planning target volume was 25 Gy. For the gamma limit, a peripheral dose of 20 Gy to the 50% isodose was allowed. Isodose limits were 75% (maximum diameter) for single metastases and 25% for multiple metastases. Dose limits for targets of the same metastases were followed by SRS. The SRS dose was prescribed to the tumor margin. Metastatic tumors with a maximum diameter of up to 2 cm were treated with 22–25 Gy, and those metastases larger than 2 cm were treated with 18–29 Gy. The dose reduced by 5% when the treatment was combined with WBRT.

Aoyama et al.

Kocher et al.

Brown et al.
Local Control After SRS?

% Failure

Andrews 2004

Kocher 2011

Local Failure rate ~ 30%
Higher? However Brown et al. intracranial progression not initial site only

Edward Shaw et al. Red J. 2000

Accrual by treatment arm and dose

<table>
<thead>
<tr>
<th>Tumor diameter</th>
<th>Treatment arm/dose/accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20 mm</td>
<td>Arm 1 -&gt; Arm 4 -&gt; Arm 7</td>
</tr>
<tr>
<td></td>
<td>18 Gy 21 Gy 24 Gy</td>
</tr>
<tr>
<td>21-30 mm</td>
<td>Arm 2 -&gt; Arm 5 -&gt; Arm 8</td>
</tr>
<tr>
<td></td>
<td>15 Gy 18 Gy 21 Gy 24 Gy</td>
</tr>
<tr>
<td>31-40 mm</td>
<td>Arm 3 -&gt; Arm 6 -&gt; Arm 9</td>
</tr>
<tr>
<td></td>
<td>12 Gy 15 Gy 18 Gy</td>
</tr>
<tr>
<td></td>
<td>n = 21 n = 22 n = 18</td>
</tr>
</tbody>
</table>

RTOG CNS Toxicity criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild neurologic symptoms; no medication required</td>
</tr>
<tr>
<td>2</td>
<td>Moderate neurologic symptoms; outpatient medication required (e.g., steroids)</td>
</tr>
<tr>
<td>3</td>
<td>Severe neurologic symptoms; outpatient or inpatient medication required</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening neurologic symptoms (e.g., uncontrolled seizures, paralysis, or coma); includes clinically or radiographically suspected radiation necrosis and histologically proven radiation necrosis at the time of an operation</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>
Results RTOG 90-05

Imaging response

<table>
<thead>
<tr>
<th>Change versus baseline</th>
<th>Imaging response (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 mos</td>
</tr>
<tr>
<td>Complete response</td>
<td>4</td>
</tr>
<tr>
<td>Improved</td>
<td>38</td>
</tr>
<tr>
<td>Unchanged</td>
<td>42</td>
</tr>
<tr>
<td>Worse</td>
<td>16</td>
</tr>
</tbody>
</table>

Failure pattern
- Any In-Volume (Local): 40%
- Local alone: 27%
- Local + adjacent to target volume: 6%
- Local + non-adjacent intracranial: 3%
- Local + adjacent to target volume + non-adjacent intracranial: 3%

Incidence of Grade 3, 4, 5 CNS toxicity

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Arms</th>
<th>Dose</th>
<th>No. of patients</th>
<th>% of Patients With Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20 mm</td>
<td>1</td>
<td>18 Gy</td>
<td>12</td>
<td>0 0 8</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21 Gy</td>
<td>18</td>
<td>0 11 11</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>24 Gy</td>
<td>10</td>
<td>0 10 10</td>
</tr>
<tr>
<td>21–30 mm</td>
<td>2</td>
<td>15 Gy</td>
<td>15</td>
<td>7 7 13</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>18 Gy</td>
<td>15</td>
<td>0 20 20</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>21 Gy</td>
<td>13</td>
<td>8 31 38</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>24 Gy</td>
<td>12</td>
<td>33 25 58</td>
</tr>
<tr>
<td>31–40 mm</td>
<td>3</td>
<td>12 Gy</td>
<td>21</td>
<td>5 5 10</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>15 Gy</td>
<td>22</td>
<td>0 14 14</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>18 Gy</td>
<td>18</td>
<td>17 33 50</td>
</tr>
</tbody>
</table>

Conclusions: The maximum tolerated doses of single fraction radiosurgery were defined for this population of patients as 24 Gy, 18 Gy, and 15 Gy for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in maximum diameter. Unacceptable CNS toxicity was more likely in patients with larger tumors, whereas local tumor control was most dependent on the type of recurrent tumor and the treatment unit. © 2000 Elsevier Science Inc.

Influence of Dose Prescription on LC?

Patients treated on a line had a 2.84 times higher risk of local tumor progression compared to those who underwent Gamma Knife radiosurgery, despite having a more favorable Gamma Knife radiosurgery. As seen in Table 4: 94% of Gamma Knife treated patients had an MD/PD ratio of two, since dose was prescribed to the 50% isodose line. This results in a dose gradient of 100% from the center of the tumor to the periphery, that is, there are internal “hot spots.”

While such inhomogeneity is undesirable in standard, large field external beam radiation therapy, it may have effectively boosted the central, hypoxic, more radiosistent portion of the tumor, accounting for the better local control.

Edward Shaw et al. Red J. 2000
Variation in SRS-Dose: 3 prescription approaches

60 Gy prescribed to center of target
Target
60 Gy prescribed to isocenter
Peripheral dose ~ 57 Gy

60 Gy prescribed to periphery of target (80%)
Target
iso center dose 75 Gy
Peripheral dose 60 Gy (80%)

60 Gy prescribed to periphery of target (60%)
Target
iso center dose 100 Gy
Peripheral dose 60 Gy (60%)

COLDEST TREATMENT
Tumor covered by 57 Gy

INTERMEDIATE:
Tumor covered by 60 Gy
Maximum dose 75 Gy

HOTTEST TREATMENT:
Tumor covered by 60 Gy
Maximum dose 100 Gy

Senan et al. 2011

Influence of prescription models

8mm diameter met treated with a single 8mm collimator to 25 Gy

90% coverage
Dmax = 30.1 Gy

95% coverage
Dmax = 31.6 Gy

100% coverage
Dmax = 35.7 Gy

1mm margin
Dmax = 44.6 Gy

48% Difference in dose

Courtesy Ian Paddick

ESTRO School
Influence of prescription models

Nr. 15

Two lesions, both treated to 25 Gy covering 97% of target

8 mm diameter lesion
8 mm Collimator
25 Gy @ 80%
Peak Dose = 31.3 Gy
Mean Dose = 27.5 Gy

11 mm diameter lesion
8 mm Collimator
25 Gy @ 50%
Peak Dose = 50 Gy
Mean Dose = 35 Gy

Conformity Index ?!

Nr. 16

A number of alternative conformity indices have been suggested over the past decade. The conformity index put forward by the RTOG has been widely in use since its introduction in 1993. This index has been criticized for its lack of consideration of the spatial overlap of the target and treated volumes. Subsequently, modifications to the RTOG conformity index have been proposed by groups such as Paddick to account for spatial overlap. This overlap was calculated using the geometric overlap ratio. 89% of the examined targets the geometric overlap ratio was greater than 0.8, which suggests that as clinically used plans, the information provided by this ratio is not critical for evaluating plan quality provided a dose distribution is available for visual inspection. Most of the time, routine clinical planning results in geometrically overlapping

\[ CI_{RTOG} = \frac{TV}{PV} \]

Conformity Index

\[ CI = \frac{\text{Volume of target covered by PI}}{\text{Volume of target covered by PI}} \times \frac{\text{Volume of PI}}{\text{Volume of Target \text{Over/Under treatment ratio}} \times \text{Volume of Target \text{Under/Over treatment ratio}} \times \text{Volume of Target}} \]

\[ CI = 1.0 \text{ represents perfect conformity} \]

Gradient Index

\[ GI = \frac{\text{Volume of isodose that is } \% \text{ of PI}}{\text{Volume of PI}} \]

\[ GI \leq 3.0 \text{ is “good” dose fall off} \]

19.12.16
**Dose-Response**

Dose–effect relation in stereotactic radiotherapy for brain metastases. A systematic review

**RS- data sets (12 months)**

**FSRS- data sets (12 months)**

Local control: It’s Dose, Volume and Conformity Index!

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**Multiple Brain Metastases**

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

Masaaki Yamamoto*, Toru Seizawa*, Takashi Shuto, Atsuyo Akabane, Yoshihito Higuchi, Jun Kawagishi, Kazuhiro Yamada, Yosunori Sato

- 1194 patients in total
- 455 patients with 1 met
- 531 patients with 2-4 mets
- 208 patients with 5-10 mets

Results:
- SRS without WBRT in patients with five to ten brain metastases is non-inferior to that in patients with two to four brain metastases.
- Considering the minimal invasiveness of stereotactic radiosurgery and the fewer side effects than with WBRT, stereotactic radiosurgery might be a suitable alternative for patients with up to ten brain metastases
Multiple Brain Metastases

<table>
<thead>
<tr>
<th>Group</th>
<th>Median overall survival, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tumour</td>
<td>13.9 (12.0-15.6)</td>
<td>0.76 (0.66-0.88)</td>
<td>0.0004</td>
</tr>
<tr>
<td>2-4 tumours</td>
<td>16.8 (9.4-22.4)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>5-10 tumours</td>
<td>16.8 (9.3-13.7)</td>
<td>0.27 (0.93-1.18)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

How to do it?

- Traditionally Gamma Knife (GK) based
- Linac – based: criticism whether “single-isocenter VMAT” will allow comparable plans (clinically and dosimetry) to GK-Quality
How to do it?

- One Isocenter?
- How many lesions?
- Time on table?

Brainlab Elements Software

- CT und MR Data will be registered automatically.
- While this takes place, organs at risk will be segmented automatically based on the MRI.
- Contouring of the mets can be done in an easy and fast way using Smartbrush.
By using templates, different fractionation schemes, margins and prescription doses can be chosen.
Clinical Case Report

ED 05/2009
06/2009 Excision and SLND left axilla (+)
07/2009 left axilla diss. (0/10)
11/2014 Lung Metastases
11/2014 Resection of 3 lung-mets
01/2015 ED Brain Metastases
01-03/2015 4 Cycles Ipilimumab
04/2015 Progress cerebral and systemic (Liver)
04/2015 Dabrofinib
Radiotherapy

1 x 23 Gy
7 lesions

MRT 10/2016: only 2 visible (smaller) lesions, PDL-1 systemic treatment

Dose response for „side effects“

Long-term risk of radionecrosis and imaging changes after stereotactic radiosurgery for brain metastases

271 brain metastases treated with single-fraction linac based srs

Actuarial incidence of radionecrosis stratified by tumor diameter

Kohutek et al.

J Neurooncol. 2015 October
Treatment Response Assessment Maps

- Unique method for neuro-oncological decision-making
- Providing conclusive information about tumor status
- Differentiates tumor progression from treatment effects
- Identifying treatment effects, like pseudo-progression and tumor necrosis
- Developed at Sheba Medical Center with Brainlab technology

BLUE = Tumor

RED = Pseudo Progression

MRI 1 @3min post Gd

MRI 2 @70min post Gd
**TRAM**

**Nr. 29**

**Delayed contrast extravasation MRI: a new paradigm in neuro-oncology**

Histological validation
Brain metastases
47 underwent resection
Relative cerebral blood volume maps

**Conclusions.** The TRAMs present a novel model-independent approach providing efficient separation between tumor/nontumor tissues by adding a short MRI scan >3 h post contrast injection. The methodology uses robust acquisition sequences, providing high resolution and easy to interpret maps with minimal sensitivity to susceptibility artifacts. The presented results provide histological validation of the TRAMs and demonstrate their potential contribution to the management of brain tumor patients.

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**Summary**

**Nr. 30**

**It` s not a numbers game !**

Treatment decisions must be individualized based on a complex array of both patient-specific and tumor-specific characteristics

- SRS should be considered in patients with 1-3 brain metastases (and more....).
- WBRT improves local control but not survival when added to SRS (effect maybe different in different entities/subgroups).
- Precise dose prescription protocols necessary in SRS for the future
Thanks for your attention!