Title: CNS Metastases

Name: Philip Poortmans
Radiation Oncologist

Date: 25 November 2019

Former President

President
DISCLOSURES
I have nothing to disclose
CNS METASTASES

1. Introduction

2. Standard treatment

3. Increasing efficacy

4. Preventing side effects

5. Conclusions
Facts that you probably know – epidemiology:

✓ Brain metastases ~ 10 times more common than primary CNS Tumours

✓ Overall occurring in ± 20-30 % of cancer patients (increasing trend)

✓ Depending on primary tumour side: lung (30 - 80%), breast (5 – 35%), melanoma (5 - 75%), renal (5.5 - 11%), colorectal (1.4 - 4.8%)

✓ Depending on histology and molecular subtype: lung ➔ SCLC/adenocarcinoma; breast ➔ HER2 positive/triple negative/PI3K/mTOR pathway mutations (?); melanoma ➔ mucosal melanoma/acral lentiginous or nodular/BRAF or NRAS mutations
Facts that you probably know - epidemiology:

Breast cancer specific:

✓ Up to 0.5 % of patients have brain metastases at the time of initial diagnosis
✓ Most brain metastases are diagnosed after diagnosis of systemic spread elsewhere
✓ Most frequent 1 to 3 years after initial diagnosis

Martin et al. 2017; Steeg et al. 2011; Villano et al. 2015
Facts that you probably know – diagnosis:

✓ Brain MRI is the best diagnostic tool to detect brain metastases.

✓ Standard MRI includes T2-weighted, pre- and post-gadolinium-enhanced T1-weighted sequences and a post contrast fluid-attenuated inversion-recovery (FLAIR) sequence.

✓ Is tissue evaluation necessary?
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➔ 54 single brain “metastasis” patients with known systemic cancer having surgery before WBRT ➔ 6 (11%) had glioblastoma, LG astrocytoma, abscess, or inflammation....

➔ Imaging much improved to aid in diagnosis... but mind the DD of enhancing brain lesions!
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➔ Imaging much improved to aid in diagnosis... but mind the DD of enhancing brain lesions!
Facts that you probably know – diagnosis:

Discrepancies between biomarkers of primary breast cancer and subsequent brain metastases: an international multicenter study

O. Kaidar-Person¹,²,³ · I. Meattini⁴ · P. Jain⁵ · P. Bult⁶ · N. Simone⁷ · I. Kindts⁸,⁹ · R. Steffens¹⁰ · C. Weltens⁸,⁹ · P. Navarria¹¹ · Y. Belkacemi¹² · J. Lopez-Guerra¹³ · L. Livi⁴ · B. G. Baumert¹⁰,¹⁹ · B. Vieites¹⁴ · D. Limon¹⁵ · N. Kurman¹⁵ · K. Ko⁷ · J. B. Yu⁵ · V. Chiang¹⁶ · P. Poortmans¹⁷,¹⁸ · T. Zagar¹,²

➔ Oh yes, also this: 20% of patients had a receptor discrepancy between the primary tumour and subsequent BM.

Facts that you probably know – prognosis:

Recursive partitioning analysis (RPA):

✓ RPA class 1: age <65; KPS ≥70, controlled primary, no extracranial metastases
✓ RPA class 2: “the others”
✓ RPA class 3: KPS <70

OS:

7.1m
4.2m
2.3m
Facts that you probably know – prognosis:

✓ Disease-Specific Graded Prognostic Assessment (GPA) published 2010.

✓ Sub-scores of 0 to 1 for each factor (age, KPS, number of metastases, and extracranial disease) ➔ summed to determine GPA score ranging 0 – 4.

✓ Validated by a multi-institutional retrospective analysis of 4259 other patients with brain metastases treated with WBRT and/or SRS.
Facts that you probably know – prognosis:

<table>
<thead>
<tr>
<th>Breast cancer</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic Factor</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>60</td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal</td>
<td>n/a</td>
</tr>
<tr>
<td>Age, years</td>
<td>≥ 60</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Sperduto et al. 2012
CNS METASTASES: INTRODUCTION

Facts that you probably know – prognosis:

✓ These analyses date from the past...
✓ ... a lot has changed...
✓ ... the future is yet to come.
CNS METASTASES

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CNS METASTASES: STANDARD TREATMENT

Corticosteroids

➢ Alleviate symptoms from oedema in >75%.
➢ Dexamethasone - low mineralocorticoid activity and T1/2 ~ 36-54 hours.
➢ Absorbed readily P.O.
➢ Randomized trial ➔ 4 to 8 mg as effective as 16 mg.
➢ Symptoms improve within hours; max benefit after ~ 3 to 7 days.
➢ Severe mass effects symptoms or no response <48h ➔ higher doses.
➢ After asymptomatic or maximal benefit ➔ dose gradually tapered to lowest dose level needed to manage symptoms (best = nothing).

We give too much steroids! Do not start steroids if CNS Lymphoma is suspected!!!
CNS METASTASES: STANDARD TREATMENT

Facts that you probably know – treatment:

✓ Until recently whole brain RT (WBRT) was the standard of care

✓ Pretty independent from RT schedule

✓ This worked ...

✓ ... temporarily

✓ And causes hair loss ...

✓ ... for those patients who had still hair

RTOG 1979-1993: 3 consecutive trials with > 1100 patients
CNS METASTASES: STANDARD TREATMENT

No treatment
OS 1 month

Best supportive care
OS 2.5 months

Adapted from Orit Kaidar-Person; Lang 1964; Markesbery 1978; Order 1968
CNS METASTASES: STANDARD TREATMENT

No treatment
OS 1 month

Best supportive care
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1950s & 1960s WBRT
60% symptomatic improvement
OS 3-6 months

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Today: Patients with Brain metastases can live several years
Not a single entity, even within the same histology

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OS 1 month

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OS 2.5 months

1950s & 1960s WBRT
60% symptomatic improvement
OS 3-6 months

Today: Patients with Brain metastases can live several years
Not a single entity, even within the same histology

Survival according to Disease Specific- Graded Prognosis Assessment (DS-GPA) score:

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>mOS (months)</th>
<th>GPA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>14</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Adapted from Orit Kaidar-Person; Lang 1964; Markesbery 1978; Order 1968; Sperduto et al. 2012
### Results of stereotactic radiosurgery (SRS) for brain metastases

<table>
<thead>
<tr>
<th>Reference</th>
<th>n(patients/lesions)</th>
<th>Prescribed dose (median; range [Gy])*</th>
<th>Median OS (m)</th>
<th>1-year PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirzkall et al. 1998 [28]</td>
<td>236/311</td>
<td>20; 10-30</td>
<td>5.5</td>
<td>89</td>
</tr>
<tr>
<td>Cho et al. 1998 [81]</td>
<td>73/136</td>
<td>17.5; 6-50</td>
<td>7.8</td>
<td>80</td>
</tr>
<tr>
<td>Sneed et al. 1999 [27]</td>
<td>62/118&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18; 15-22</td>
<td>11.3</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>43/117&lt;sup&gt;b&lt;/sup&gt;</td>
<td>17.5; 15-22</td>
<td>11.1</td>
<td>86</td>
</tr>
<tr>
<td>Varlotto et al. 2003 [82]</td>
<td>137/208</td>
<td>16; 12-25</td>
<td>Not given</td>
<td>90</td>
</tr>
<tr>
<td>Andrews et al. 2004 [18]</td>
<td>164/269&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Not given; 15-24</td>
<td>6.5</td>
<td>82</td>
</tr>
<tr>
<td>Bhatnagar et al. 2006 [83]</td>
<td>205/4-18 lesions each&lt;sup&gt;d&lt;/sup&gt;</td>
<td>16; 12-20</td>
<td>8.0</td>
<td>71</td>
</tr>
</tbody>
</table>
Still up to 20-30% of the so called “good patients” (1 to 3 brain mets all <3 cm) die within 3 months of SRS (Brown et al., JAMA 2016)
CNS METASTASES: STANDARD TREATMENT

Courtesy O. Kaidar-Person.
CNS METASTASES: STANDARD TREATMENT

Multidisciplinary approach:
✓ Neurosurgeons,
✓ Neuro-oncology,
✓ Radiation Oncology
✓ Medical Oncology
✓ Shared decision-making
CNS METASTASES

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CNS METASTASES: INCREASING EFFICACY

Radiation Therapy:

✓ Whole Brain Radiation Therapy (WBRT)

✓ Stereotactic Radiation Therapy (SRT)

✓ Single fraction

✓ Fractionated Stereotactic Radiation Therapy (f)SRT

⇒ (sf)SRT
CNS METASTASES: INCREASING EFFICACY

Radiation Therapy - WBRT vs. SRT:

✓ Efficacy

✓ Toxicity

✓ Convenient for patients

✓ Costs

✓ Easy to implement
**CNS METASTASES: INCREASING EFFICACY**

Radiation Therapy - WBRT vs. SRT:

- ✓ Convenient for patients

<table>
<thead>
<tr>
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<th>WBRT</th>
<th>SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be treated</td>
<td>Can be treated immediately, minimal time for planning</td>
<td>Needs an updated MRI with contrast, CT-SIM, Fusion, meticulous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>delineation and planning, QA verification</td>
</tr>
<tr>
<td>Treatment time</td>
<td>~ 12 minutes</td>
<td>Treatment time depending on the number of mets, method used, dose,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 - 75 minutes</td>
</tr>
<tr>
<td>* Delays systemic</td>
<td></td>
<td>* Minimal interference with systemic therapy</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Courtesy O. Kaidar-Person.
CNS METASTASES: INCREASING EFFICACY

Radiation Therapy - WBRT vs. SRT:

✓ Easy to implement

• WBRT has the advantage of being widely available, can be initiate quickly w/o complicated planning, treats both gross and subclinical disease, and provides palliation for symptoms
  • Concern: toxicity, mainly cognitive decline

• SRT frameless mask can be implemented in most centers after appropriate training of the staff. It needs meticulous planning and QA procedures.
  • Concern: costs, radiation necrosis
CNS METASTASES: INCREASING EFFICACY

Radiation Therapy - WBRT vs. SRT:

✓ Efficacy

✓ Toxicity

✓ Convenient for patients

✓ Costs

✓ Easy to implement

➢ Local control

➢ Distant intracranial control

➢ Overall survival
Radiation Therapy - WBRT vs. SRT:

- WBRT – trials ➔ CR-rate per lesion = ±24%.
- WBRT – trials ➔ (CR+PR)-rates; 50% for non-breast adeno; 46% for RCC, and 0% for melanoma.
- Response rates are associated with volume of metastases.
CNS METASTASES: INCREASING EFFICACY  Limited disease

Radiation Therapy - WBRT vs. SRT:

<table>
<thead>
<tr>
<th></th>
<th>WBRT</th>
<th>SRT</th>
<th>WBRT+SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local control</td>
<td>71%@1yr</td>
<td>67-73%@1yr</td>
<td>83-100%@1yr</td>
</tr>
<tr>
<td>Distant intracranial</td>
<td>94.6%@6m 89.2%@1yr</td>
<td>76.7%@6m 69.9%@1yr</td>
<td>94.7%@6m 92.3%@1yr</td>
</tr>
<tr>
<td>control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall survival</td>
<td>No sign differences</td>
<td>No sign differences</td>
<td>No sign differences</td>
</tr>
</tbody>
</table>

Radiation Therapy – SRT after surgery:

✓ 1-year local control is around 82% for SRS/FSRT to resection cavity.

✓ 1-year distant intracranial control is ~ 54%.

✓ No differences in OS.

Gans et al., 2013; Kaidar-Person, 2016
CNS METASTASES: INCREASING EFFICACY  Limited disease

Radiation Therapy - WBRT vs. SRT single lesion postoperative:

Postoperative SRT compared with WBRT for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial:

<table>
<thead>
<tr>
<th>Indicator</th>
<th>SRT</th>
<th>WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC @ 6m</td>
<td>80.4%</td>
<td>87.1%</td>
</tr>
<tr>
<td>LC @12m</td>
<td>61%</td>
<td>81%</td>
</tr>
<tr>
<td>OS (med)</td>
<td>12.2m</td>
<td>11.6m</td>
</tr>
</tbody>
</table>
CNS METASTASES: INCREASING EFFICACY  Limited disease

Radiation Therapy - WBRT vs. SRT:

<table>
<thead>
<tr>
<th></th>
<th>SRS</th>
<th>WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>at 3 months</td>
<td>79.6% (72.0, 88.0)</td>
<td>90.4% (84.7, 96.6)</td>
</tr>
<tr>
<td>at 6 months</td>
<td>55.1% (46.1, 65.9)</td>
<td>80.8% (73.1, 89.2)</td>
</tr>
<tr>
<td>at 12 months</td>
<td>36.6% (28.1, 47.8)</td>
<td>72.1% (63.6, 81.8)</td>
</tr>
</tbody>
</table>

*SRS vs. WBRT: p < 0.0001*

CNS METASTASES: INCREASING EFFICACY  Limited disease

Radiation Therapy - WBRT vs. SRT:

Association of neurosurgical resection with development of pachymeningeal seeding in patients with brain metastases:

➢ Cohort study of 1188 patients ➔ surgery + SRT vs. RT alone
➢ Surgery + SRT ➔ increased meningeal seeding
  ➢ surgery + SRT: 36/318 patients
  ➢ RT alone: 0/870 patients

\[ P < 0.001 \]

Cagney DN et al. JAMA Oncol 2019.
CNS METASTASES: INCREASING EFFICACY  Limited disease
CNS METASTASES: INCREASING EFFICACY  Limited disease

Clinical Investigation

Consensus Contouring Guidelines for Postoperative Completely Resected Cavity Stereotactic Radiosurgery for Brain Metastases

CNS METASTASES: INCREASING EFFICACY  Limited disease

Doubts about treatment choice surgery + RT vs. SRT alone:
✓ No prospective randomized trials ... studies suggest similar LC and OS
✓ Surgery might induce meningeal spreading, depending on location, histology, etcetera
✓ RT most often required after surgery
✓ Tumour bed is tricky to delineate
✓ Efficacy increases if we choose wisely patients for each modality
✓ Including upfront systemic therapy +/- surgery +/- SRT +/- WBRT
✓ Disease Specific – Graded Prognosis Analysis (DS-GPA)
✓ Best supportive care remains always an option!
Doubts about treatment choice surgery + RT vs. SRT alone:

Prefer surgery if:

✓ Need for tissue confirmation
✓ To relieve mass effect from a large symptomatic lesion
✓ More durable local control for a single metastasis > 3 cm?
✓ Salvaging locally recurrent metastasis

Prefer SRT alone if:

✓ Multiple metastases
✓ Contraindication for resection: location; size; ...
✓ Indication for fast initiation systemic therapy

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**When is WBRT indicated for limited brain metastases:**

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<thead>
<tr>
<th>First Author/Years</th>
<th>Treatment</th>
<th>n</th>
<th>ECM(%)</th>
<th>LC (mo)</th>
<th>Median Survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews 1996-2001 (Andrews et al., 2004)</td>
<td>WBRT</td>
<td>167</td>
<td>69</td>
<td>[71% at 1 yr]</td>
<td>5.7</td>
</tr>
<tr>
<td></td>
<td>WBRT + SRS</td>
<td>164</td>
<td>68</td>
<td>[82% at 1 yr]</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>(37.5 Gy/15 fx)</td>
<td></td>
<td></td>
<td>(P = 0.013)</td>
<td>(P = .136)</td>
</tr>
<tr>
<td>Aoyama 1999-2003 (Aoyama et al., 2006)</td>
<td>SRS</td>
<td>67</td>
<td>43</td>
<td>[73% at 1 yr]</td>
<td>8.0</td>
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<td>37</td>
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<tr>
<td></td>
<td>(30 Gy/10 fx)</td>
<td></td>
<td></td>
<td>(P = .002)</td>
<td>(P = .42)</td>
</tr>
<tr>
<td>Chang 2001-2007 (Chang et al., 2009)</td>
<td>SRS</td>
<td>30</td>
<td>—</td>
<td>[67% at 1 yr]</td>
<td>15.2</td>
</tr>
<tr>
<td></td>
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<td>28</td>
<td>—</td>
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</tr>
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<td>Kocher 1996-2007 (Kocher et al., 2011)</td>
<td>SRS</td>
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<td>—</td>
<td>[69% at 2 yr]</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>79</td>
<td>—</td>
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<td>Brown et al., 2016</td>
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<td>[72.8% at 1 yr]</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>SRS + WBRT</td>
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<td>75</td>
<td>[90.1% at 1 yr]</td>
<td>7.4</td>
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</tbody>
</table>
WBRT after SRT or surgery adds to LC and Intracranial control, but does not add to OS (> 80% die from systemic disease) and reduces neurocognitive function.
### CNS METASTASES: INCREASING EFFICACY  Limited disease

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</tr>
<tr>
<td>Kocher 1996-2001</td>
<td>SRS</td>
<td>100</td>
<td>—</td>
<td>[67% at 2 yr]</td>
<td>10.9</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
<td>79</td>
<td>—</td>
<td>[41% at 2 yr]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Combined SRS + WBRT</td>
<td>99</td>
<td>—</td>
<td>[81% at 2 yr]</td>
<td>10.7</td>
</tr>
<tr>
<td></td>
<td>Surgery + WBRT</td>
<td>81</td>
<td>—</td>
<td>[73% at 2 yr]</td>
<td>Combined</td>
</tr>
<tr>
<td></td>
<td>(30 Gy/10 fx)</td>
<td></td>
<td></td>
<td></td>
<td>(P = .012)</td>
</tr>
<tr>
<td>Brown et al., 2016</td>
<td>SRS</td>
<td>111</td>
<td>81</td>
<td>[72.8% at 1 yr]</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>SRS+WBRT</td>
<td>102</td>
<td>75</td>
<td>[90.1% at 1 yr]</td>
<td>7.4</td>
</tr>
</tbody>
</table>

**Nevertheless, individual patients (young; limited number/volume of brain metastases) might benefit from additional WBRT...**

*Sahgal et al. 2015*
Uncertainty about WBRT alone vs. SRT + WBRT vs. SRT alone:

- Randomized trials assessing SRT ± WBRT excluded patients with > 3-4 metastases.

Increasing use of SRT with postponing of WBRT:

- Increased availability and quality of SRT
- Desire to avoid side effects of WBRT
- Non-invasive immobilisation allowing for fSRT (larger targets, multiple targets)
Uncertainty about WBRT alone vs. SRT + WBRT vs. SRT alone:

✓ JLGK0901 evaluated SRT in 1194 patients with 1 to 10 brain metastases who were treated with SRS alone (initially).

✓ Largest lesion <10 cc (~2.7 cm), total tumour volume <15 cc; no evidence of leptomeningeal disease; KPS >70.

✓ 3% of Grade 3-4 (no diff between the groups)

<table>
<thead>
<tr>
<th>N Brain mets (n pts)</th>
<th>mOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (455)</td>
<td>13.9 [95% CI 12-15.6]</td>
</tr>
<tr>
<td>2-4 (531)</td>
<td>10.8 [95% CI 9.4-12.4]</td>
</tr>
<tr>
<td>5-10 (208)</td>
<td>10.8 [95% CI 9.1-12.7]</td>
</tr>
</tbody>
</table>

No difference in survival

Serizawa et al. 2010; Yamamoto et al. 2014.
CNS METASTASES: INCREASING EFFICACY

Extensive disease

MOST cases: WBRT is initial treatment with SRT as salvage
SRS for ≥ 4 metastases should be considered in case of:
✓ Small brain metastases
✓ No evidence of systemic disease
✓ Radioresistant tumours with controlled (or minimal) systemic disease.

Courtesy O. Kaidar-Person. Brown et al. JCO 2018
CNS METASTASES: INCREASING EFFICACY

Role of systemic therapy for brain metastases:

Table 2. Selected Prospective Trials of Systemic Therapies in the Treatment of Brain Metastases, Intracranial Response Rate, Intracranial Progression-Free Survival, and Overall Survival

<table>
<thead>
<tr>
<th>Drug Studied</th>
<th>Phase</th>
<th>No. of Patients With Brain Metastases</th>
<th>Key Study Features</th>
<th>Median ICRR (%)</th>
<th>Median ICPFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib (Dummer et al.36)</td>
<td>I+II</td>
<td>Cohort A: 89446666; 74</td>
<td>Cohort A: Treatment naive</td>
<td>39.2</td>
<td>4 months (16.1 weeks)</td>
<td>8.2 months (33.1 weeks)</td>
</tr>
</tbody>
</table>

Table 2. Selected Prospective Trials of Systemic Therapies in the Treatment of Brain Metastases, Intracranial Response Rate, Intracranial Progression-Free Survival, and Overall Survival

<table>
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<th>Median ICPFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lapatinib plus capecitabine (Bachelot et al.40)</td>
<td>II</td>
<td>45</td>
<td>Treatment naive</td>
<td>65.9</td>
<td>5.5 months</td>
<td>17 months</td>
</tr>
<tr>
<td>Lapatinib (Lin et al.)41</td>
<td>II</td>
<td>242</td>
<td>Previously treated</td>
<td>6</td>
<td>2.4 months</td>
<td>6.4 months</td>
</tr>
<tr>
<td>Neratinib (Freedman et al.42)</td>
<td>II</td>
<td>40</td>
<td>Previously treated</td>
<td>—</td>
<td>1.9 months</td>
<td>8.7 months</td>
</tr>
</tbody>
</table>

Abbreviations: ICPFS, intracranial progression-free survival; ICRR, intracranial response rate; NR, not reported; OS, overall survival; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiotherapy. Overall progression-free survival.
We miss data to define for which patients we can defer RT.
CNS METASTASES: INCREASING EFFICACY  Extensive disease

New treatments for brain metastases:

Targeting the PI3K/Akt/mTOR pathway with the pan-Akt inhibitor GDC-0068 in PIK3CA-mutant breast cancer brain metastases.

Ippen FM$^{1,2}$, Grosch JK$^{1,2}$, Subramanian M$^3$, Kuter BM$^1$, Liederer BM$^3$, Plise EG$^3$, Mora JL$^1$, Nayar N$^1$, Schmidt SP$^4$, Giobbie-Hurder A$^5$, Martinez-Lage M$^6$, Cancers (Basel). 2019 May 13;11(5). pii: E665. doi: 10.3390/cancers11050665.

A Comparison of DNA Mutation and Copy Number Profiles of Primary Breast Cancers and Paired Brain Metastases for Identifying Clinically Relevant Genetic Alterations in Brain Metastases.


The Dual PI3K/mTOR Pathway Inhibitor GDC-0084 Achieves Antitumor Activity in PIK3CA-Mutant Breast Cancer Brain Metastases.


Phase Ib/II single-arm trial evaluating the combination of everolimus, lapatinib and capecitabine for the treatment of HER2-positive breast cancer with brain metastases (TRIO-US B-09).

Hurvitz S$^1$, Singh R$^2$, Adams B$^3$, Taguchi JA$^4$, Chan D$^6$, Dicke RA$^6$, Castrellon A$^7$, Hu E$^3$, Berkowitz J$^6$, Mani A$^7$, Dicarlo B$^8$, Callahan R$^3$, Smales J$^9$, Wang X$^3$, Meglar I$^3$, Martinez D$^3$, Hobbs E$^3$, Slamon DJ$^3$. 
CNS METASTASES: INCREASING EFFICACY  Extensive disease

New treatments for brain metastases:


Effect of Tumor-Treating Fields Plus Maintenance Temozolomide Alone on Survival in Glioblastoma: A Randomized Clinical Trial

New treatments for brain metastases:

Still a lot of work for young researchers!
CNS METASTASES

1. Introduction

2. Standard treatment

3. Increasing efficacy

4. Preventing side effects

5. Conclusions
## CNS METASTASES: PREVENTING SIDE EFFECTS

### Side effects after treatment for brain metastases:

<table>
<thead>
<tr>
<th>WBRT</th>
<th>SRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hair loss</td>
<td>• Brain necrosis</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Hair loss</td>
</tr>
<tr>
<td>• Cognitive impairment (PCI)</td>
<td>• Cognitive impairment*</td>
</tr>
<tr>
<td>• Xerostomia</td>
<td>• Vision loss, hearing loss, endocrine function</td>
</tr>
<tr>
<td>• Hearing loss</td>
<td>• More…</td>
</tr>
<tr>
<td>• Reduction of QOL</td>
<td></td>
</tr>
</tbody>
</table>

Mostly unavoidable

**Common protocols** 30Gy/10fx, 20Gy/5fx

Unavoidable versus poor RT planning

Highly dependent on the location, dose/fx, previous RT, systemic therapy, etc

---

Side effects after treatment for brain metastases:

Cognitive decline after WBRT:
✓ DD with intracranial progression, depression, fatigue, steroid withdrawal
✓ Donepezil (acetylcholinesterase inhibitor)
Side effects after treatment for brain metastases:

**Neurocognitive toxicity from WBRT:**
- Related to doses > 3.5 Gy per fraction
- Higher total doses
- Elderly (mostly with pre-exciting cognitive decline, vascular disease, DM)
- Disabling dementia after WBRT < 5 %
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Reducing toxicity:
✓ Hippocampal sparing
✓ Memantine (N-methyl-D-aspartate receptor antag)
✓ ACEi (?)
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Courtesy O. Kaidar-Person.
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Courtesy O. Kaidar-Person.
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Courtesy O. Kaidar-Person.
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Whole Brain Field-in-Field

EZFluence automatically generates custom segments for patient’s plans. The user sets how many segments desired for each field.

Courtesy O. Kaidar-Person.
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

More homogenous plan

Courtesy O. Kaidar-Person.
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Prescribed dose 20 Gy

Blue = 1 Gy

Courtesy O. Kaidar-Person.
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Blue = 5 Gy

Courtesy O. Kaidar-Person.
Side effects after treatment for brain metastases:
CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

_Hippocampal spearing_

Blue = 12 Gy
Light blue = 25 Gy
Green = 30 Gy

CNS METASTASES: PREVENTING SIDE EFFECTS

Side effects after treatment for brain metastases:

Assessment of Risk of Xerostomia After Whole-Brain Radiation Therapy and Association With Parotid Dose

A, Delivered radiation fields for an enrolled patient who developed persistent xerostomia. The parotids were not prospectively delineated and the parotid V20Gy was 54%. B, Alternative plan with fields adjusted to reduce parotid exposure, resulting in a parotid V20Gy of only 23%. The volume of brain covered by 95% of prescription dose was 99.98% for the original plan, compared with 99.65% for the replan.

Courtesy O. Kaidar-Person; Wang K, et al. JAMA Onc. 2019
CNS METASTASES

1. Introduction
2. Standard treatment
3. Increasing efficacy
4. Preventing side effects

5. Conclusions
Brain metastasis is no longer a “single entity”

So treatment should be individualised!
CNS METASTASES: CONCLUSIONS

Brain Metastases

Tumour related:
✓ Histology/Molecular
✓ Number of mets
✓ Mets Size
✓ Cumulative met vol

Patient related:
✓ Symptoms, Edema
✓ Age
✓ Performance status
✓ comorbidities

Disease related:
✓ Status of Systemic disease
✓ Number/Type of systemic therapy

Surgical resection -/+ SRT/WBRT/Posterior fossa RT
SRT +/- WBRT
Systemic therapy +/- SRT/+-WBRT
Best supportive care
Tumour treating fields?

Adapted from O. Kaidar-Person.
CNS METASTASES: CONCLUSIONS
CNS METASTASES: CONCLUSIONS

Brain Metastases
Multidisciplinary approach & shared decision with the patient

MEDICAL BAG

Courtesy O. Kaidar-Person.
CNS METASTASES: ACKNOWLEDGEMENTS

- The organising team of this great meeting
- My colleagues = RO’s & all others!!!!!!
- Colleagues of EORTC and ESTRO
- Our patients
- Orit Kaidar-Person
- Icro Meattini
- Brigitta Baumert
- Nicolaus Andratschke
- And many others!