The Interdisciplinary Challenge of Brain Metastases and the Role of Surgery

Manfred Westphal et al.

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UK Hamburg Eppendorf
THERAPY OF BRAIN METASTASES - THE SCOPE OF THE PROBLEM -

Current approaches to the treatment of metastatic brain tumours

Taofeek K. Owonikoko, Jack Arbiser, Amelia Zelnak, Hui-Kuo G. Shu, Hyunsuk Shim, Adam M. Robin, Steven N. Kalkanis, Timothy G. Whitsett, Bodour Salhia, Nhan L. Tran, Timothy Ryken, Michael K. Moore, Kathleen M. Egan, and Jeffrey J. Olson

The global prevalence of brain metastases in patients with cancer is probably around 8.5–9.6\textsuperscript{5,6} On the basis of data from patients recorded in the Metropolitan Detroit Cancer Surveillance System between 1973 and 2001, the most common primary tumours responsible for brain metastases are lung cancer (19.9\%), melanoma (6.9\%), renal cancer (6.5\%), breast cancer (5.1\%) and colorectal cancer (1.8\%).\textsuperscript{6}

On the basis of an official census of nearly 310 million people in the USA,\textsuperscript{1} the expected incidence of newly diagnosed patients with brain metastases is estimated to be between 21,651 to 43,301 per year.\textsuperscript{2}
Origins of Metastatic Traits

Sakari Vanharanta¹ and Joan Massague¹,2,*
THERAPY OF BRAIN METASTASES
- THE CLINICAL PROBLEM -

- INSUFFICIENT EFFICACY OF SYSTEMIC THERAPIES
Neurosurgeroy is embedded in a comprehensive individual oncological concept.

Neurosurgeroy looks at the whole spectrum of cancer, as do other “generalists”.
Surgery for Brain Metastases: Environment

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


and executed, making it less informative. In summary, there is limited class I evidence for survival benefit of surgical resection in addition to WBRT, and this is likely to be restricted to the subgroup of patients with controlled systemic disease and good performance status.

Surgical resection allows in the majority of patients an immediate relief of symptoms of intracranial hypertension, a reduction of focal neurological deficits and seizures, and a rapid steroid taper. Surgery vs Stereotactic Radiosurgery

Most studies comparing surgery and SRS report similar outcomes; however, they are not randomized and are likely to be affected by selection bias (class IIIb). SRS is considered less invasive, can be carried out in an outpatient setting, and is more cost-effective than surgery. Patients with larger lesions may require chronic steroid administration.
Surgery for Brain Metastases: WHY??

- Decompression, Mass Effect
- Establish the Diagnosis: 20% CUP
- Local Control
- Preparatory Measure for further therapy
- Assessment of tumor evolution
  - Genetic
  - Target evasion
- Any two of the above
Surgery for Brain Metastases: Establish Diagnosis

2008

Endocrine Carcinoma

2013
Surgery for Brain Metastases: Establish Diagnosis
Surgery for Brain Metastases: Establish Diagnosis

2016 CUP: Melanoma after CT and WBRT 2017
4 Weeks post-partum, one seizure
possibly angiofibroma ??
DIAGNOSTICS:

- CONTRAST MRI IS MANDATORY
- SINGULAR AND IRREGULAR: GLIOMA

GBM with recent history of Colon Carcinoma
DIAGNOSTICS:

- CONTRAST MRI IS MANDATORY
- SINGULAR AND IRREGULAR: GLIOMA
DIAGNOSTICS:

- CONTRAST MRI IS MANDATORY
- MULTIPLICITY SPEAKS FOR METS
- but not always—
Lymphoma before Corticosteroid Therapy
Lymphoma after Corticosteroid Therapy
PERIVENTRICULAR, HYPERDENSE AND “SOFT EDGES“ : LYMPHOMA
DIAGNOSTICS:

- CONTRAST MRI IS MANDATORY
- SINGULAR AND "SPHERICAL": METASTASIS
The role of surgical resection in patients with brain metastases

Mustafa Aziz Hatiboglu¹, David M Wildrick² and Raymond Sawaya²

Table 1: Randomised clinical trials comparing WBRT with and without surgery to treat brain metastases.

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Number of patients</th>
<th>Median survival time (months)</th>
<th>P</th>
<th>Local recurrence</th>
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<tbody>
<tr>
<td>Patchell et al [11]</td>
<td>WBRT</td>
<td>23</td>
<td>3.5</td>
<td>&lt;0.01</td>
<td>52%</td>
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<tr>
<td></td>
<td>WBRT+surgery</td>
<td>25</td>
<td>9.2</td>
<td></td>
<td>20%</td>
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<tr>
<td>Vecht et al [12]</td>
<td>WBRT</td>
<td>31</td>
<td>6</td>
<td>0.04</td>
<td>N/A</td>
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<tr>
<td></td>
<td>WBRT+surgery</td>
<td>32</td>
<td>10</td>
<td></td>
<td>N/A</td>
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</table>

WBRT, whole-brain radiation therapy
Surgery for Brain Metastases: Local Control

Solitary Metastasis of NSCLC
Surgery for Brain Metastases: Local Control
Metastasis of Thyroid carcinoma after radiosurgery AND resection
Surgical removal of metastasis of mammary carcinoma plus radiation

**Pre Op**
12.7.01

**Post Op**
7.1.02

Surgery for Brain Metastases : Local Control
Metastasis of mammary carcinoma

pre op  After resection and + 45 Gy. WBRT
Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial

Alexander Muacevic · Berndt Wowra · Axel Siefert · Joerg-Christian Tonn · Hans-Jakob Steiger · Friedrich W. Kreth

**Fig. 3** Graph illustrating the local tumor control rates after surgery and radiosurgery. The difference was not statistically significant

**Fig. 4** Graph illustrating the distant brain tumor control rates. Distant brain tumor control was statistically significant higher in the surgery group
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 D 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, Shaan Raza, Nandita Guha-Thakurta, James Yang, Raymond Sawaya, Kenneth R Hess, Ganesh Rao

Methods In this randomised, controlled, phase 3 trial, we recruited patients at a single tertiary cancer centre in the USA. Eligible patients were older than 3 years, had a Karnofsky Performance Score of 70 or higher, were able to have an MRI scan, and had a complete resection of one to three brain metastases (with a maximum diameter of the resection cavity ≤4 cm). Patients were randomly assigned (1:1) with a block size of four to either SRS of the resection cavity (within 30 days of surgery) or observation. Patients were stratified by histology of the primary tumour, metastatic tumour size, and number of metastases. The primary endpoint was time to local recurrence in the resection cavity, assessed by blinded central review of brain MRI scans by the study neuroradiologist in the modified
Surgery for Brain Metastases: Local Control

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

Anita Mehrotra, Salman Ahmed, Mary Francis McAllister, Jeffrey S Weinberg, Jing Li, Paul D Brown, Stephen Settle, Suji S Pothu, Frederick F Lang, Nicholas Levine, Susan McGovern, Erik Salmon, Ian E McCutcheon, Syed Azeem, Daniel Cohill, Claudio Tatsui, Amy B Holmberger, Shervin Fargues, Arnold Chio, Franco Bersante, Simon Ross, Naandito Gokhale-Thakkar, James Yang, Raymond Sereys, Kenneth R Hess, Ganesh Rad
Simultaneous Resection of Multiple Metastatic Brain Tumors with Multiple Keyhole Craniotomies

Cordell Michael Baker¹, Chad A. Glenn¹, Robert G. Briggs¹, Joshua D. Burks¹, Adam D. Smitherman¹, Andrew K. Conner¹, Allison E. Williams¹, Muhammad U. Malik¹, Ozer Algan², Michael E. Sughrue¹

Table 1. Patient and Tumor Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>Median age, years (Range)</th>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>11</td>
<td>55 (27–75)</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>58 (48–74)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>57 (27–75)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>(5%)</td>
</tr>
<tr>
<td>Colon</td>
<td>1</td>
<td>(5%)</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>(60%)</td>
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Table 2. Operative Information

<table>
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<th>Number of Craniotomies</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>2</td>
<td>18 (90)</td>
</tr>
<tr>
<td>3</td>
<td>1 (5)</td>
</tr>
<tr>
<td>4</td>
<td>1 (5)</td>
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</table>

Table 5. Mortality and Surgical Outcomes

<table>
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<tr>
<th>Cumulative Survival at</th>
<th>Patient Survival</th>
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<tbody>
<tr>
<td>3 months</td>
<td>77%</td>
</tr>
<tr>
<td>6 months</td>
<td>69%</td>
</tr>
<tr>
<td>9 months</td>
<td>53%</td>
</tr>
<tr>
<td>12 months</td>
<td>46%</td>
</tr>
<tr>
<td>18 months</td>
<td>31%</td>
</tr>
<tr>
<td>Median survival</td>
<td>10.8 months</td>
</tr>
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</table>
Simultaneous surgery for multiple lesions?
Simultaneous surgery for multiple lesions?
Simultaneous surgery for multiple lesions?
SURGERY POST SRS ? OR WAIT AND WATCH ?
Acute Situation: Incapacitating Disturbance of Coordination; 10 yrs Colon Carcinoma, Age 45

Surgery for Brain Metastases: Decompression
Acute Situation: Hemorrhagic Metastasis - Melanoma
Surgery for Brain Metastases: Decompression

Acute Situation: Hemorrhagic Metastasis - Melanoma
Subsequent Radiation Necrosis, Lambrolizumab - What to do ???
Radionecrosis induced by stereotactic radiosurgery of brain metastases: results of surgery and outcome of disease

Stefano Telera · Alessandra Fabi · Andrea Pace · Antonello Vidiri · Vincenzo Anelli · Carmine Maria Carapella · Laura Marucci · Francesco Crispo · Isabella Sperduti · Alfredo Pompili
In toto vs piecemeal: Complications

Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis

*Akash J. Patel, MD,1,2 Dima Suki, PhD,1 Mustafa Aziz Hatiboglu, MD,1 Vikas Y. Rao, MD,2 Benjamin D. Fox, MD,1 and Raymond Sawaya, MD1,2

TABLE 4. Overall 30-day complications and complications according to surgical method in patients who underwent surgery for a single previously untreated brain metastasis*
In toto vs piecemeal: Seeding

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 242)</th>
<th>En Bloc (n = 87)</th>
<th>Piecemeal (n = 155)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>144 (60)</td>
<td>44 (51)</td>
<td>100 (65)</td>
</tr>
<tr>
<td>female</td>
<td>98 (40)</td>
<td>43 (49)</td>
<td>55 (35)</td>
</tr>
<tr>
<td><strong>age</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>median</td>
<td>60.5</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>range</td>
<td>19–88</td>
<td>26–88</td>
<td>19–77</td>
</tr>
<tr>
<td><strong>primary cancer</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>breast</td>
<td>25 (10)</td>
<td>13 (15)</td>
<td>12 (8)</td>
</tr>
<tr>
<td>lung</td>
<td>104 (66)</td>
<td>58 (67)</td>
<td>106 (68)</td>
</tr>
<tr>
<td>other</td>
<td>53 (22)</td>
<td>16 (18)</td>
<td>37 (24)</td>
</tr>
</tbody>
</table>

Risk for leptomeningeal seeding after resection for brain metastases: implication of tumor location with mode of resection

Clinical article

Jun Hyong Ahn, M.D., Sang Hyun Lee, M.D., Ph.D., Sohee Kim, M.S., Jungnam Joo, Ph.D., Heon Yoo, M.D., Ph.D., Seung Hoon Lee, M.D., Ph.D., Sang Hoon Shin, M.D., and Ho-Shin Gwak, M.D., Ph.D.
Three years post-OP bilateral occipital Mets from Mammary Carcinoma
Meningeal carcinomatosis after stereotactic biopsy for small cell bronchial carcinoma
**Review Article**

**Current Standards in the Management of Cerebral Metastases**

Pablo Goetz,¹ Julius O. Ebinu,¹ David Roberge,² and Gelareh Zadeh¹

<table>
<thead>
<tr>
<th>RPA 97²</th>
<th>Routine WBRT after surgery</th>
<th>WBRT + SRS boost</th>
<th>WBRT after SRS</th>
<th>Neuro cognition concerns: withholding WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>WBRT</td>
<td>Surgery + WBRT</td>
<td>1990¹</td>
<td>1998³</td>
</tr>
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</table>

1. Patchell et al. [24]
2. Gaspar et al. [6]
3. Patchell et al. [28]
4. Kondziolka et al. [38]
5. Andrews et al. [36]
6. Aoyama et al. [39]
7. Chang et al. [40]
8. Kocher et al.—EORTC [15]

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*International Journal of Surgical Oncology*  
Volume 2012, Article ID 493426, 9 pages  
doi:10.1155/2012/493426
Brain Metastasis: Clinical Implications of Branched Evolution

Ibiyi Dagogo-Jack, Scott L. Carter, and Priscilla K. Brastianos

Key Figure

Tumor Evolution in Primary Tumor and Matched Brain Metastases (BM)

Normal cell (germline)

Primary tumor

Brain metastasis

Tissue collection

Time

Figure 1. The figure shows a representation of tumor evolution and tissue-sampling scenario consistent with primary and matched BM. Vertical lines indicate hypothetical tissue-sampling proportions of cancer and normal cells. This scenario implies that genetic characterization of primary tumor biopsies will result in tissue-sampling bias, whereby mutations in the BM are not present in the primary tumor biopsy, and vice versa. Reproduced, with permission, from Brastianos et al. [30].
### Clinical Pathway - Hirnmetastasen

#### Basisprogramm
- Klinisch-neurologische Untersuchung
- Hirndruckzeichen
- Extrazerebrale Tumormanifestationen
- MRT Schädel mit KM
- CT Schädel mit KM bei Kontraindikationen gegen MRT
- CT Schädelbasis bei Frage nach Knocheninfiltration
- Ggf. Liquoruntersuchung

#### Argumente für Operation:
- Singuläre oder solitäre Metastase
  - Guter Allgemeinzustand (KPS 70-100%)
  - Geringe neurologische Defizite
  - Keine oder stabile (> 3 Monate) extrakranielle Tumormanifestationen
  - Unbekannter Primärtumor
  - Neuroradiologisch nicht sicher als Metastase einzuordnende Läsion
  - Operativ gut zugängliche Läsion
  - Raumfordernde Metastase (> 3 cm)
  - Infratentorielle Lokalisation mit drohendem Liquoraufstau
  - Kein hohes Risiko schwerer neurologischer Defizite durch die Operation
  - Relevanz molekularer Testung des Metastasengewebes
  - Längeres Intervall (> 4 Jahre) zur Diagnose des Primärtumors

#### Interdisziplinäre Therapieentscheidung

#### Argumente für fraktionierte Ganzhir恩bestrahlung:
- Multiple Hirnmetastaser
  - 1-4 Metastasen, die nicht für Operation oder Radiochirurgie in Frage kommen
  - Kontrovers: adjuvant nach Resektion einzelner Metastasen
  - Progrediente extrazerebrale Tumormanifestationen, insbesondere bei weniger chemotherapieempfindlichen Tumoren (wahrscheinliche Lebenserwartung > 3 Monate)
  - Bei kleinzelligem Bronchialkarzinom als Teil des multimodal Therapiekonzepts und prophylaktisch
  - Bei Keimzelltumoren als Teil des multimodal Therapiekonzepts

#### Nachsorge:
- MRT (CCT bei Kontraindikationen) alle 3 Monate oder nach Klinik
- Überprüfung Indikation zur Steroidtherapie
- Überprüfung Indikation zur Behandlung mit Antikonvulsiva
- Endokrinologische Untersuchung bei Hinweis auf Hypophyseninsuffizienz

#### Supportive Therapie
- Steroide, z.B.
  - Dexamethason 4-8 mg/d („so viel wie nötig, so wenig wie möglich“)
- Ggf. Antikonvulsiva
- Ggf. primäre prophylaktische antikonvulsive Therapie bei erhöhtem intrakraniellen Druck und multiplen Knochenmetastasen
- Physiotherapie, Ergotherapie, Logopädie
- Palliativmedizinische Massnahmen

#### Foundation tumour:
- Inspektion der Haut
- Röntgen Thorax
- Thorax-CT
- Mammographie
- Abdomensonographie mit Darstellung der Nieren
- Ggf. Osophago-gastro-duodenoskopie und Koloskopie
- Ggf. CT Abdomen und Becken
- alternativ FDG-PET als primäre Diagnostik
Argumente für Operation:

- Singuläre oder solitäre Metastase
- Guter Allgemeinzustand (KPS 70-100 %)
- Geringe neurologische Defizite
- keine oder stabile (> 3 Monate) extrakranielle Tumormanifestationen
- Unbekannter Primärtumor
- Neuroradiologisch nicht sicher als Metastase einzuordnende Läsion
- Operativ gut zugängliche Läsion
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- Längeres Intervall (> 4 Jahre) zur Diagnose des Primärtumors
Review Article

The Role of Radiation Therapy in the Management of Metastatic Melanoma in the Brain

Angela Hong,1,2,3 Gerald Fogarty,1,2,4 and Michael A. Izard2,4,5

Newly diagnosed brain metastases

Manage symptoms and assess prognostic factors

Suitable for treatment

Single or oligometastases

Surgery or stereotactic radiosurgery

+/− Adjuvant whole brain radiation therapy

Multiple metastases

Whole brain radiation therapy

Not suitable for anti cancer treatment

Palliative support
BRAIN METASTASES
- DECISION MAKING I -

PRIMARY TUMOR KNOWN

TUMOR STAGING

NO OPTION FOR SYSTEMIC THERAPY FOR BM

Therapy

No Therapy

MRI

3 Lesions or less

Karnofsky > 70
Stable disease, therapeutic options
Life expectancy > 3 mo
Surgery possible

SURGERY or SRS

MRI

> 3 Lesions

SURGERY for symptomatic lesion?
WBRT SRS

ONCOLOGIST

RADIOThERAPY
Management of Spinal Metastases

Microsurgical Removal
BEYOND TREATMENT OPTIONS
NO INDICATION FOR SURGERY DUE TO HERNIATION AND FAR PROGRESSION OF UNDERLYING DISEASE
NO INDICATION FOR SURGERY DUE TO HERNIATION AND FAR PROGRESSION OF UNDERLYING DISEASE
Surgery for Brain Metastases: WHY??

- Decompression, Mass Effect
- Establish the Diagnosis: 20% CUP
- Local Control
- Preparatory Measure for further therapy
- Assessment of tumor evolution
  - Genetic
  - Target evasion
- Any two of the above
Spinal Meningeal Carcinomatosis

- End of the Line -
Gadolinium Visualized Convection

- Bronchial Carcinoma Metastasis -

male 54 y
Safety and efficacy of carmustine (BCNU) wafers for metastatic brain tumors

Chibawanye I. Ene, John D. Nerva, Ryan P Morton, Ariana S. Barkley, Jason K. Barber, Andrew L. Ko, Daniel L. Silberfeld

<table>
<thead>
<tr>
<th>Table 3: Survival data</th>
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<td></td>
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<tr>
<td>Age</td>
</tr>
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<tr>
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