Metastatic Disease to the Brain, Spine, Carcinomatous Meningitis

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DISCLOSURES

Off-Label Usage
  • Rituximab (Genentech)

Interests
  • None
Covering

- (Parenchymal) brain metastases
- Epidural spinal cord compression
- Intramedullary spinal cord metastases
- Neoplastic meningitis
## Brain Metastases - Epidemiology

- **Incidence unknown: 10-20% of cancer pts**
  - Thought to be increasing
  - Most common primaries
    - Lung 40-50%
    - Breast 15-20%
    - Melanoma, renal, GI 5-10% each

### Likelihood with different primary tumors
- Melanoma 18-90%
- Lung 18-65%
- Breast 20-30%
- Gastrointestinal 1-10%
- Ovarian 3%
- Prostate 1%
Brain Mets – Clinical Presentation

- 90% known cancer, 10% synchronous (2/3 lung)
- Common symptoms
  - Headache 50%
  - Focal weakness 30%
  - Mental status changes 32%
  - Gait ataxia 20%
  - Seizures 20%
- Common signs
  - Hemiparesis 60%
  - Mental status changes 60%
Brain Metastases: Imaging

- MRI superior to CT
- With/without contrast
- # lesions: 25% 1, 25% 2-3, 50% 4+
- Single lesion
  - Hx cancer: 90% likely metastatic
  - No hx cancer: 15% chance metastasis
    - CT C/A/P or body PET-CT
Not Brain Mets
Brain Metastases: Prognosis

- Median survival 4 mo
- Most deaths 2º systemic disease
- RTOG RPA classes
  - 1 (7.1 mo): age < 65, 1º controlled, no extracranial mets, KPS > 70
  - 2 (4.2 mo): Not Class 1 or 3
  - 3 (2.3 mo): KPS ≤ 70

L Gaspar, IJROBP, 1997
Brain Mets: Supportive Treatment

- **Corticosteroids**
  - Improve symptoms in ≈ 2/3, add ≈ 1 mo to OS
  - Mild symptoms: low doses suffice (DXM 2 bid)
  - Severe symptoms/herniation: 16-24 mg/day

- **Anticonvulsants**
  - For the 20% of patients with seizures
  - No role for prophylactic anticonvulsants
  - Stick to non-P450 inducers

- **Memantine** – improves cognitive outcome

- **Venous thromboembolic disease**
  - Common – treat with anticoagulation (preferably LMWH?) unless mets are frankly hemorrhagic
Brain Mets: Whole Brain Radiotherapy

- Treats all mets, visible and microscopic
  - Choice of schedules
- Inexpensive and technologically simple
- Most effective for radiosensitive histologies
- ≈ 60% CR/PR rate
- Drawbacks
  - Fatigue
  - Leukoencephalopathy and risk of dementia
  - Eventual local relapse
  - Radioresistant tumors
Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial
RTOG 0614 Schema

Brain Metastasis

**STRATIFY**

- RPA Class I
- RPA Class II*

**RANDOMIZE**

- 20 mg Memantine Daily
- Placebo

WBRT 37.5Gy in 15 fractions

*with stable systemic disease

Memantine started ≤ 3 days of RT Continued 24 weeks, even if PD

1° endpoint: HVLT Delayed Recall at 24 weeks
Results

• 554 patients
• Primary endpoint: just missed (p=0.059)
  – 35% power with 149 analyzable patients at 24 weeks
• Other findings
  – Memantine delays time to cognitive decline
  – Reduces decline in memory, executive function and processing speed
Why Avoid the Hippocampus? A Comprehensive Review

Vinai Gondi, M.D.*, Wolfgang A. Tomé, Ph.D.*, &, and Minesh P. Mehta, M.D.*

PHYSICS CONTRIBUTION

HIPPOCAMPAL-SPARING WHOLE-BRAIN RADIOTHERAPY: A “HOW-TO” TECHNIQUE USING HELICAL TOMOTHERAPY AND LINEAR ACCELERATOR–BASED INTENSITY-MODULATED RADIOTHERAPY

Vinai Gondi, M.D.*, Ranjini Tolakanahalli, M.S.,† Minesh P. Mehta, M.D.*, Dinesh Tewatia, M.S.,*† Howard Rowley, M.D.,† John S. Kuo, M.D., Ph.D.,*† Deepak Khuntia, M.D.,* and Wolfgang A. Tomé, Ph.D.*†

Whole brain radiotherapy

Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: Safety profile for RTOG 0933

Vinai Gondi a*, Wolfgang A. Tome a,b, James Marsh e, Aaron Struck a, Amol Ghia a, Julius V. Turian e, Søren M. Bentzen a,c, John S. Kuo a,d, Deepak Khuntia a, Minesh P. Mehta a
RTOG 0933

- Phase II study of HA-WBRT
  - 100 pts
  - Primary endpoint: HVLT-DR at 4 mo
  - Historical WBRT control group

- Results
  - Highly significant preservation of delayed recall
    - 7% vs 30% decline on HVLT-DR at 4 mo
  - 5% failed in hippocampal avoidance region

- Plan for phase III confirmatory trial in SCLC PCI

ASTRO 2013, courtesy of Vinai Gondi
Brain Mets: Craniotomy/Resection

• Improves survival c/w WBRT for single brain met in better prognosis pts (Patchell NEJM)
  – <65, controlled systemic disease, good PS

• After metastatectomy, WBRT ↓s the risk of both local and remote brain failure (Patchell JAMA)
Brain Mets: Radiosurgery (RS)

- Multiple convergent beams/arcs to met
  - Gamma Knife, LINAC
- Best for mets ≤ 3 cm median diameter
- Can treat surgically inaccessible mets
- Local control 70-90% at one year
  - Much better than WBRT for radioresistant mets
- As add-on to WBRT
  - ↑s local control
  - Improves OS for pts with single brain met
Brain Mets: RS alone or with WBRT?

- 3 published randomized studies
  - Restricted to pts with 1 to 3-4 brain mets

- Consistent conclusions
  - WBRT improves local control at RS sites
  - WBRT improves remote intracranial control
    - More salvage therapy needed in RS alone group
  - WBRT does not improve overall survival
    - <30% of brain met pts die from brain mets

- No evidence yet that WBRT improves cognitive function or QoL (modest evidence to contrary)
NCCTG N0574: Phase III

Primary endpoint:
Neurocog/QOL

Sample Size: 168

Translational correlates
- Serial QOL
- Neurocognitive assessments

1-3 Brain Mets on MRI

Radiosurgery (RS)
20-24 Gy

RS 18-22 Gy → WBRT (30 Gy)

PROG
Case

• 57F with node+ breast ca diagnosed in 2000
  – Prior “AC”, RT, Taxol, Herceptin, Tamoxifen
• Presented with HA 10/04
  – Exam: tactile hemineglect
  – Systemic staging negative
Resection of Metastasis

- 2000 cGy in 5 fractions to cavity margins

Post-op scan 11-04
9 Years Later

- No cognitive sequelae – continues to teach

September 2013
Focal Radiation to Surgical Cavity

• 14 published series; only 2 prospective; none RCT

TABLE 1. Study Characteristics of Stereotactic Radiosurgery After Resection of Brain Metastases

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients, n</th>
<th>Median Follow-up, mo</th>
<th>RPA Class I, %</th>
<th>RPA Class II, %</th>
<th>RPA Class III, %</th>
<th>GTR, %</th>
<th>Median Margin Dose, Gy</th>
<th>Median OS, mo</th>
<th>Crude LC, %</th>
<th>1-y LC, %</th>
<th>Distant Recurrence, %</th>
<th>Salvage WBRT, %</th>
<th>Complications, %</th>
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<td>Solty et al, 2008</td>
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GTR, gross total resection; LC, local control; NR, not reported; RPA, recursive partitioned analysis; OS, overall survival; WBRT, whole-brain radiotherapy.
NCCTG N107C
SRS to Resection Margins vs. WBRT

- Resected Brain Met

**STRATIFY**
- Age <60 vs. >60
- # Brain Mets 1 vs. 2-4
- Extracranial Dz
- Histology Lung vs. Radioresistant vs. Others
- Surgical Cavity <3 vs. >3cm

**RANDOMIZE**
- SRS Surgical Bed +SRS unresect mets
- WBRT* + SRS unresected mets

*37.5 Gy/15
Limitations of Studies

- Histology matters
- OS a flawed endpoint
- PFS
  - Pseudoprogression and pseudoresponse
  - Treatment toxicity
- Response: RECIST? Macdonald?
  - Compartment issues and mixed response
- Multidimensional endpoints needed
Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group

Nancy U Lin, Eudocia Q Lee, Hidesumi Aoyama, Igor J Barani, Brigitta G Baumert, Paul D Brown, D Ross Camidge, Susan M Chang, Janet Dancey, Laurie E Gaspar, Gordon J Harris, F Stephen Hodi, Steven N Kalkanis, Kathleen R Lamborn, Mark E Linkey, David R MacDonald, Kim Mangolin, Minesh P Mehta, David Schiff, Riccardo Soffietti, John H Suh, Martin J van den Bent, Michael A Vogelbaum, Jeffrey S Wofld, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

Therapeutic outcomes for patients with brain metastases need to improve. A critical review of trials specifically addressing brain metastases shows key issues that could prevent acceptance of results by regulatory agencies.

Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group

Nancy U Lin, Jeffrey S Wofld, Eudocia Q Lee, David Schiff, Martin J van den Bent, Riccardo Soffietti, John H Suh, Michael A Vogelbaum, Minesh P Mehta, Janet Dancey, Mark E Linkey, D Ross Camidge, Hidesumi Aoyama, Paul D Brown, Susan M Chang, Steven N Kalkanis, Igor J Barani, Brigitta G Baumert, Laurie E Gaspar, F Stephen Hodi, David R MacDonald, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group

Neurocognitive function, neurological symptoms, functional independence, and health-related quality of life are
Epidural Spinal Cord Compression (ESCC)

- Compression of thecal sac that may deform spinal cord or cauda equina
- Affects 3-5% of pts with cancer
- May arise from any cancer
  - Breast, lung, prostate 15-20% each
  - NHL, myeloma, RCC other common causes
- In 20%, initial manifestation of cancer
  - Lung, NHL, myeloma
- 60% in thoracic and 30% lumbosacral spine
- 90% vertebral mets; 10% paraspinous mass
ESCC: Symptoms and Signs

- Back pain: 90-95%, typically for 2-3 mo
  - Gradually worsening, may \( \uparrow \) w/recumbency
  - Often, radicular component over time
  - Abrupt worsening suggests compression fracture
- Motor: Weakness in 65-80% at diagnosis
  - Usually symmetric; findings depend on level
- Sensory loss: Majority of patients
  - Requires careful history and exam
  - Level typically 1-5 levels below anatomic compression
- Bowel/bladder dysfunction: Late finding
  - Rarely the sole symptom of ESCC
- Majority of patients non-ambulatory at diagnosis
ESCC: Radiographic Diagnosis

- MRI the best
  - Images cord, leptomeninges, bone, paraspinal tissues
  - Coagulopathy, low platelets, spinal block not concerns
- CT-myelography
  - Alternative when MRI contraindicated
  - May be adjunct in (radio)surgical planning
  - May be easier for pts with severe pain
- CT: Good for bone destruction but doesn’t show cord, epidural space
- Plain x-rays: not sensitive enough for screening tool
  - Vert collapse or pedicle erosion highly predictive of ESCC
- One-third of pts have multiple ESCCs
ESCC Treatment: Supportive Care

- Corticosteroids
  - Beneficial in animal models and human trials
  - Optimal dose unknown: more SEs with ↑ dose
    - Pain + minimal neuro dysfunction 16 mg/d
    - Moderate-severe dysfunction – 100 mg daily
      - Taper by 50% every 3 days
    - No neuro dysfunction, minimal ESCC: no steroids?
- Analgesia: Steroids + opiates
  - Vertebro/kyphoplasty: generally not for epidural disease
- Bowel regimen
- DVT prophylaxis
- Enforced bed rest and bracing unnecessary
ESCC: Fractionated RT

- Standard of care for most patients
- Selection of radiation ports
- Potential side effects
  - Radiation myelopathy
  - Gastrointestinal
  - Myelosuppression
ESCC: Neurologic Outcome after RT

- Pre-treatment ambulatory status
  - 80-100% amb post-Rx if amb pre-Rx
  - 1/3 amb post-Rx if paraparetic pre-Rx
  - 2-6% amb post-Rx if paraplegic pre-Rx

- Tumor type

- Rapidity of onset of deficits also a factor
  - Rapid onset of deficits over $\leq 48^\circ$ bodes poorly

- Degree of spinal block (↓↓ importance)

- $\approx 50\%$ alive at one year still ambulatory
ESCC: RT Dose & Schedule

• RCT of 1600 cGy/2 fx vs 3,000 cGy/8 fx
  – Randomized 300 pts with life expectancy < 6 mo.
  – No differences in efficacy or toxicity

• 3,000/10 vs 4,000/20
  – Prospective but Rx assigned based on appt availability
  – No difference in post-Rx motor fx or % ambulatory

• 1,300 pts on 5 schedules (800/1 to 4,000/20)
  – Retrospective
  – All regimens gave similar functional results
  – More protracted schedules had fewer in-field recurrences
  – Recommended 800/1 for poor prognosis and 3,000/10 for good prognosis

ESCC: Surgery

• Laminectomy w/o stabilization best avoided
• Replaced by radical resection + stabilization
• Case series suggested best initial Rx for
  – Spinal instability
  – Retropulsed bone in spinal canal
  – Deterioration during/after RT
  – Radioresistant tumor and otherwise good prognosis
ESCC: Surgery + RT vs. RT

- RCT for non-radiosensitive metastatic ESCC
  - Direct circumferential tumor resection + RT vs RT only
  - RT 3,000 cGy in 10 fractions
  - RT only arm could cross over to S for worsening
  - 1º endpoint time ambulatory after treatment
- Single ESCC, life expectancy 3+ mo, no paraplegia > 48º
- Surgical complication rate 12%
- 9/16 non-ambulatory pts in S/RT group regained ability to walk c/w 3/16 in RT group
- 20% of RT group crossed over to S/RT because of deterioration during RT
Surgery + RT: median 126 days
RT-alone: median 35 days
RR=0.55 (95%CI, 0.35-0.86)
P=0.006, log rank
ESCC: Radiosurgery

- A.k.a. stereotactic body radiotherapy
- Precision allows ↑ tumor dose while sparing cord
- Requires immobilization, control for respiratory movement, incorporation of CT scanner and LINAC
- Particularly useful for radioresistant tumors
  - RCC, sarcoma, melanoma
- Achieves long-term tumor control in ≈ 90% w/o neuro deficits or spinal instability
- However, larger tumors producing high-grade cord compression can’t be safely and effectively treated without first debulking
- Reasonable 1st option in low-grade ESCC from radioresistant tumor w/o spinal instability
ESCC: Chemotherapy

- Viable primary option if the tumor is predictably chemosensitive
- Hormonal Rx for breast and prostate cancer
- Cytotoxic chemo for lymphoma, germ cell, neuroblastoma
ESCC: Managing Recurrence

• 20% recur at median of 7 mo
  – Half at initial site of ESCC
  – Half of 2-yr survivors of ESCC have 2nd episode
• Radiosurgery good option if lesion small
• Standard RT reasonably effective especially if life expectancy < 1 yr
• Surgical decompression if prognosis adequate
• Systemic therapy?
Intramedullary Spinal Cord Mets

- Diagnosis increasing 2° MRI
- $\approx 50\%$ lung ca (esp SCLC); breast, renal, lymphoma, melanoma also common
- Brown-Sequard syndrome
- Less likely than ESCC to be associated with pain
- Majority have brain mets, $\frac{1}{4}$ meningeal ca
- Treatment typically steroids and RT
  - Usually stabilizes neurologic function, but OS poor
Intramedullary Spinal Cord Mets
Leptomeningeal Disease (LMD): Epidemiology

- 1-8% of patients on autopsy studies
- Breast, lung, lymphoma, leukemia, melanoma
- Usually with known metastatic disease
- Brain met hx in 70% of solid tumor pts
LMD: Clinical Features

- Multifocal subacute neurologic dysfunction
  - Cerebral hemispheres (HA, HC, encephalopathy)
  - Cranial nerves/posterior fossa
  - Spinal cord/nerve roots

- Diagnosis: CSF cytology and/or MRI
  - MRI of entire neuraxis for LM enhancement
    - More sensitive for solid tumor than heme LMD
    - Occasionally unequivocally diagnostic
  - CSF: Most diagnostic but limited sensitivity
    - \( \approx 2/3 \) have + cytology with two LPs
    - CSF is rarely completely normal with LMD
LMD: MRI
LMD Treatment: Radiation

- Craniospinal RT rarely indicated
- RT palliative
  - Generally reserved for symptomatic/bulky sites
    - Skull base for CN palsies
    - Cerebral convexities for HC, encephalopathy
    - Spine, as needed
LMD Treatment: Systemic Chemotherapy

- Theoretical benefit: treats systemic tumor
- For success, requires:
  - Drug that penetrates BBB
  - Drug active against tumor
- HD MTX, ara-C achieve good CSF levels
- Capecitabine, temozolomide, thiotepa cross and are occasionally useful
LMD Treatment: Intrathecal Chemo

- Via LP or intraventricular (Ommaya) reservoir
- Minimizes systemic side effects
- Achieves high intra-CSF levels
- Little penetration into bulky deposits
- CSF block may → neurotoxicity
  - Radionuclide flow studies useful
- All agents may cause aseptic meningitis
  - Leukoencephalopathy, rarely transverse myelopathy
- Drugs: MTX, thiotepa, ara-C, liposomal ara-C
# LMD Treatment: Clinical Trials

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<tr>
<th>Study</th>
<th>Design</th>
<th>Response</th>
<th>Toxicity</th>
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<tr>
<td>Grossman et al</td>
<td>n = 59, solid tumors and lymphoma (in 90%); i.t. MTX versus thiotepa</td>
<td>i.t. MTX versus thiotepa: neurological improvements, none; median survival, 15.9 versus 14.1 wks</td>
<td>i.t. MTX versus thiotepa: serious toxicities similar between groups; mucositis and neuro complications more common in MTX group</td>
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<td>Boogerd et al</td>
<td>n = 35, breast cancer; i.t. versus no i.t. treatment (permitted RT and systemic chemo)</td>
<td>i.t. versus no i.t.: improvement or stabilization, 59% versus 67%; TTP, 23 versus 24 wks; median survival, 18.3 versus 30.3 wks</td>
<td>i.t. versus no i.t.: neurological complications, 47% versus 6%</td>
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<tr>
<td>Shapiro et al</td>
<td>Solid tumors (n = 103), DepoCyt versus MTX; lymphoma (n = 25), DepoCyt versus ara-C</td>
<td>DepoCyt versus MTX/ara-C: PFS 35 versus 43 days; DepoCyt versus MTX: PFS 35 versus 37.5 days; DepoCyt versus ara-C: CR 33.3% versus 16.7%; PFS 34 versus 50 days</td>
<td>DepoCyt versus MTX/ara-C: drug-related AEs, 48% versus 60%</td>
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<td>Glantz et al</td>
<td>n = 28, lymphoma; DepoCyt versus MTX</td>
<td>DepoCyt versus ara-C: TTP 78.5 versus 42 days (NS); OS 99.5 versus 63 days (NS); RR, 71% versus 15%</td>
<td>DepoCyt versus ara-C: headache, 27% versus 2%; nausea, 9% versus 2%; fever, 8% versus 4</td>
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<tr>
<td>Glantz et al</td>
<td>n = 61, solid tumors; DepoCyt versus MTX</td>
<td>DepoCyt versus MTX: RR 26% versus 20%; OS 105 versus 78 days; TTP 58 versus 30 days</td>
<td>DepoCyt versus MTX: sensory/motor, 4% versus 10%; altered mental status, 5% versus 2%</td>
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</table>
LMD: Prognosis & Recommendations

- Median survival ≈ 1 mo w/o, 2-3 mo w/Rx
- Sensitive tumors (heme, breast) better prognosis, but 1 yr survival 15%
- Belief that treatment palliates symptoms
- RT for bulky/symptomatic disease
- IT or systemic chemo depending on tumor type, prior Rx, systemic disease