NRG Hippocampal Avoidance Trials: CC001 and CC003
NRG CC001/CC003 Webinar: Agenda

- Welcome and Introductions – Marge Good, MPH, MHA; Program Director, National Cancer Institute Division of Cancer Prevention, Community Oncology Program

- Background on NRG CC001 and NRG CC003
  - Paul Brown, MD—NRG CC001 Co-Principal Investigator
  - Vinai Gondi, MD—NRG CC001/CC003 Co-Principal Investigator

- MRI Imaging Overview – Tammie Benzinger, MD
  - NRG CC001/CC003 Imaging Co-Chair

- RT Quality Assurance—Denise Manfredi BS, RT(T) (with Dr. Gondi)
  - Director, IROC Phila RT

- Frequently Asked Questions
Differential sensitivity of memory-related domains to radiation effects, as an early effect after WBRT
NCCTG N0574 (Alliance): A Phase III Randomized Trial of Whole Brain Radiation Therapy in Addition to Radiosurgery in Patients with 1 to 3 Brain Metastases

Presenting Author: Paul Brown, MD
MD Anderson Cancer Center

N0574 Design

1-3 Brain Mets

Stratify

- Age (18 to 59 vs. ≥ 60)
- Extra-Cranial Disease Controlled (≤ 3 vs. > 3 mo)
- Number Brain Mets (1 vs. 2 vs. 3)
- Institution

Randomize

Arm A (SRS only):
- Lesions < 2.0 cm: 24 Gy
- Lesions 2 – 2.9 cm: 20 Gy

Arm B (SRS and WBRT):
- Lesions < 2.0 cm: 22 Gy
- Lesions 2 – 2.9 cm: 18 Gy
- WBRT: 30 Gy/12

Primary Objective: Determine if cognitive progression 3 mo post-SRS is less with SRS alone than SRS combined with WBRT

Courtesy of: Paul Brown, MD
Primary Endpt: Cognitive Progression at 3 mos

<table>
<thead>
<tr>
<th></th>
<th>SRS</th>
<th>SRS+WBRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Progression at 3 months (95% CI)</td>
<td><strong>63.5%</strong> (50.5, 75.3)</td>
<td><strong>91.7%</strong> (80.0, 97.7)</td>
<td>0.0007</td>
</tr>
</tbody>
</table>

- Decline in cognitive function more frequent with the addition of WBRT to SRS
- Persisted at 6 months (SRS 77.8% vs. SRS+WBRT 97.9%, p = 0.032)
## Cognitive Deterioration at 3 months

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>SRS</th>
<th>SRS+WBRT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT Total Recall</td>
<td>8.2%</td>
<td>30.4%</td>
<td>0.0043</td>
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<tr>
<td>HVLT Delayed Recall</td>
<td>19.7%</td>
<td>51.1%</td>
<td>0.0009</td>
</tr>
<tr>
<td>HVLT Recognition</td>
<td>22.6%</td>
<td>40.4%</td>
<td>0.0585</td>
</tr>
<tr>
<td>TMT Part A</td>
<td>16.7%</td>
<td>30.4%</td>
<td>0.1063</td>
</tr>
<tr>
<td>TMT Part B</td>
<td>19.0%</td>
<td>37.2%</td>
<td>0.0677</td>
</tr>
<tr>
<td>COWA</td>
<td>1.9%</td>
<td>18.6%</td>
<td>0.0098</td>
</tr>
<tr>
<td>Pegboard-Dominant</td>
<td>29.3%</td>
<td>47.7%</td>
<td>0.0656</td>
</tr>
</tbody>
</table>

Deterioration = 1 SD drop from baseline

Courtesy of: Paul Brown, MD
Effect of WBRT on Self-Reported Cognition

- WBRT leads to decline in self-reported cognitive functioning

Soffietti R. et al. JCO, 2012
Summary of Clinical Data

- Impairment in memory function as an adverse effect of cranial irradiation
  - Early effect (3-4 months) after therapeutic or prophylactic cranial irradiation
  - Differential sensitivity of memory compared to other neurocognitive domains
  - Pertinent to patient-reported quality of life
1957: bilateral medial temporal lobectomy for relief of medically intractable epilepsy

- Severe anterograde amnesia immediately following the procedure
  - Impairment of declarative memory (conscious recollection of facts and events)
  - No effect on perception, intelligence, and motor skill learning

Scoville WB, Milner B. J Neurol Neurosurg Psychiatry, 1957

Mr. H.M. (1926-2008)
Hippocampal Physiology

- Generation of new hippocampal neurons arises from neural stem cells located in the subgranular layer of the hippocampus.
- Hippocampal neurogenesis vital to memory-related function
- Cranial RT impairs hippocampal neurogenesis and memory
  - Reversed with intra-hippocampal transplantation of neural stem cells

Gondi V, Tome WA, M Mehta, Radiother Oncol 2010
Conformal Avoidance of the Hippocampal Neural Stem Cells

- Preserve neurogenic fate of hippocampal neural stem cells.
- Preserve memory function after cranial RT

RTOG 0933

- Phase II study of HA-WBRT (30 Gy in 10 fractions)
- Primary endpoint: HVLT-delayed recall at 4 months
- Historical control: WBRT without hippocampal avoidance on a prior published phase III trial
  - 30% mean relative decline in HVLT-delayed recall from baseline to 4 months after WBRT
- Secondary Endpoints
  - Quality of life
  - Overall and progression-free survival
  - Adverse events

• Mean relative decline in HVLT-Delayed Recall from baseline to 4 months: 7.0% (95% CI: -4.7 to 18.7%)

• Significant compared to historical control: 30% ($p=0.0003$)

HVLNT Results

- Probability of HVLNT deterioration as defined by the Reliable Change Index:
  
<table>
<thead>
<tr>
<th>HVLNT</th>
<th>2 months</th>
<th>4 months</th>
<th>6 months</th>
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<tbody>
<tr>
<td>Total Recall</td>
<td>30.8%</td>
<td>19.0%</td>
<td>13.8%</td>
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<tr>
<td>Recognition</td>
<td>35.8%</td>
<td>11.9%</td>
<td>3.6%</td>
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<tr>
<td>Delayed Recall</td>
<td>30.2%</td>
<td>33.3%</td>
<td>17.2%</td>
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</table>

- MDACC phase III: Chang et al. Lancet Oncol 2009
  Probability of HVLNT Total Recall deterioration at 4 mos
  
  SRS alone 24%  SRS+WBRT 52%
QOL Results

- No decline in FACT-BR total score and brain subscale and Activities of Daily Living up to 6 mos ($p>0.05$ by fixed effects modeling)

HVL T Results

- Predictors of greater decline in HVL T-R Delayed Recall:
  - Age $\geq 60$ $\rightarrow$ $p = 0.0001$
  - At least minor neurologic symptoms at baseline $\rightarrow$ $p = 0.0033$
  - Hippocampal D100% $\rightarrow$ $p = 0.0037$

Conformal avoidance of the hippocampus during WBRT for brain metastases

- Is associated with prevention of memory decline and preservation of quality of life up to 6 months.
  - HVLT results compare favorably to historical series
- Higher hippocampal D100% predicts for greater decline in HVLT-Recall and Delayed Recall
- Can be safely administered
  - Two treatment-related Gd 3 events, No Gd 4-5 events
  - 4.5% risk of relapse in hippocampal avoidance region

HA-WBRT Off Study: Shouldn’t this be Standard of Care?

The Phase II study seems very convincing!
Success rate for positive phase III trial after a positive phase II oncology trials 8%
  • With such a low success rate validation in a phase III trial is required

HA-WBRT is not straightforward:
  • Pre-treatment centralized review:
    - 24% major deviations*
    - Emphasizes need for central review on trial

Gondi V, et al. IJROBP 2015
NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

PIs: Paul Brown (MDACC) + Vinai Gondi (Northwestern)

Basic Eligibility: Brain Mets 5mm outside hippocampus; KPS>70; MRI scan

Basic Statistical Design: Cognitive fxn failure 53.8% at 6 months with WBRT vs. 42.8% with HA-WBRT. 388 analyzable pts.

Sample Size: 518 patients

Primary endpt: Time to cognitive failure--HVLT-R, COWA, and TMT A and B

Brain Metastasis → Stratify → RPA → Prior Therapy → Randomize

- WBRT 30Gy/10 + Memantine
- HA-WBRT 30Gy/10 + Memantine
NRG CC001 Eligibility: Step 1 Registration

- Brain mets outside a 5mm margin around either hippocampus on contrast-enhanced MRI performed ≤21 days prior to Step 1 registration
  - Exception: If adjuvant WBRT after prior surgery, then visible disease not required on this MRI, but is required on pre-surgery MRI or CT scan and cannot be within 5mm of either hippocampus

- Volumetric MRI: 3DSPGR, MP-RAGE, TFE
  - Purposes: 1) Evaluate brain metastases, 2) Used for hippocampal contouring

- Primary English of French speaking, Zubrod PS 0-2
NRG CC001 Eligibility: Step 2 Registration

- Complete baseline neurocognitive assessment:
  - Hopkins Verbal Learning Test-Revised, Trailmaking tests, and Controlled Oral Word Association tests
  - Upload to NRG Oncology RAVE system for evaluation by Dr. Wefel (Neurocog Co-Chair)

- H&P, KPS, labs within 28 days prior to Step 2 registration

- Path dx of solid malignancy ≤5 yrs prior to Step 2 registration

- If prior radiosurgery or surgical resection, complete prior therapy (>14 days for surgery, >7 days for radiosurgery) prior to Step 2 registration
NRG CC001 Ineligibility Criteria

- Prior external beam RT or WBRT
- Leptomeningeal mets or brain mets from primary germ cell tumors, small cell carcinoma, unknown primary or lymphoma
- Radiographic evidence of hydrocephalus
  - Precludes accurate contouring of hippocampus
- Contraindication to MR imaging
- No cytotoxic chemotherapy during WBRT
NRG CC001 Accrual to Date

Accrual = 83 patients from 29 institutions (7 NCORP)
NRG CC003 Background

- **Neurocognitive toxicity of PCI**
  - LA-NSCLC (RTOG 0214): \(\uparrow\)ed decline in HVLT-R + -DR at 3, 6 and 12 mos after PCI vs. observation\(^1\)
  - SCLC (RTOG 0212): Std-dose PCI a/w 62% rate of chronic neurocognitive toxicity, 29% rt of HVLT-DR decline at 6 mos\(^2\)
  - RTOG 0212/0214 2ndary analysis: PCI a/w decline in HVLT and self-reported cognitive functioning\(^3\)

- **At a major academic center, only 60% of eligible SCLC patients receive PCI\(^3\)**
  - Patient and physician concerns re: cognitive toxicity were most common reason for lack of PCI delivery

- **In setting of small cell lung cancer, hippocampal relapse risk after HA-PCI estimated to be \(~5\%\)^5,\(^6\)**

\(^1\)Sun JCO 2011  \(^2\)Wolfson IJROBP 2009  \(^3\)Gondi IJROBP 2013  \(^4\)Gondi R&O 2010  \(^5\)Kundapur ASCO 2013
NRG CC003: Phase IIR/III Trial Prophylactic Cranial Irradiation with or without Hippocampal Avoidance for Small Cell Lung Cancer

**Basic Eligibility:** Small cell lung cancer; PR or CR to chemo; ECOG PS ≤ 70; MRI scan

**Statistical Design:**
- **Phase IIR:** Non-inferiority margin > 20%. 164 analyzable pts.
- **Phase III:** 29% with PCI vs. 14.5% with HA-PCI. 198 analyzable pts

**Sample Size:**
- **Phase IIR:** 172 patients
- **Phase III:** 304 patients

**Primary endpoints:**
- **Phase IIR:** Intracranial relapse rate at 12 months
- **Phase III:** HVLT-R delayed recall deterioration at 6 months

**Activated on 12/7/15, Accrual = 8 patients from 7 institutions (3 NCORP)**
NRG CC003 Eligibility: Step 1 Registration

- Histo/cyto proof of SCLC
- Defined as limited- vs. extensive-stage SCLC
  - H+P, CT or PET, Brain MRI
- Enroll >7 days and ≤56 days after completing chemotherapy (+/- thoracic radiotherapy)
- Re-stage after chemotherapy
  - The following criteria must be met: 1) No CNS mets, 2) Radiographic response to chemo in at least 1 disease site (RECIST), and 3) No progression at any site
- Volumetric MRI: 3DSPGR, MP-RAGE, TFE
  - Can be obtained post-chemotherapy to assess for response
  - Purposes: 1) Rule out brain metastases, 2) Used for hippocampal contouring
- Primary English of French speaking, Zubrod PS 0-2
NRG CC003 Eligibility: Step 2 Registration

- Complete baseline neurocognitive assessment:
  - Hopkins Verbal Learning Test-Revised, Trailmaking tests, and Controlled Oral Word Association tests
  - Upload to NRG Oncology RAVE system for evaluation by Dr. Wefel (Neurocog Co-Chair)

- HVLT-R Delayed Recall baseline raw score >2
NRG CC003 Ineligibility Criteria

- Prior RT to head or neck (except T1 glottic cancer)
- Radiographic evidence of CNS mets
- Radiographic evidence of hydrocephalus
  - Precludes accurate contouring of hippocampus
- Contraindication to MR imaging
- No concurrent chemo or anti-tumor agent during PCI
MR Imaging Overview
MRI Brain Images for the Exploratory Objectives of the CC001 and CC003 Imaging Protocols

The images are for the Exploratory Objectives of these Protocols. They will be used to evaluate MR imaging biomarkers of white matter injury and hippocampal volumetry at baseline and 6 months as potential predictors of neurocognitive decline and differential benefit from HA-WBRT as compared to WBRT.
What are the minimum MRI sequence requirements for the CC001 and CC003 studies?

- AXIAL T2 FLAIR
- 3D T1 POST-CONTRAST

**NOTE:** ALTHOUGH NOT REQUIRED AT BASELINE, A PRE CONTRAST AXIAL 3D IMAGING SEQUENCE IS STRONGLY ENCOURAGED.

Changes in hippocampal volume between baseline and 6 months cannot be measured without this sequence.
The below represents an example of a TRIAD submission with all **required** and **encouraged** MRI imaging sequences.
Incomplete TRIAD submission of MRI Brain images
*Missing required 3D post sequence*

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- **Series Description**
  - Ax DWI
  - COR FS T1+C (MEMP)
  - 3Plane Loc SSFSE
  - GRE
  - Exponential Apparent Diffusion
  - Apparent Diffusion Coefficient
  - Sag T1 FLAIR
  - AX T1 +C (MEMP)
  - AX T1 FLAIR
  - AX T2 FSE
  - AX T2 FLAIR

- **Modality**: MR
- **Imag...**: Clean
- **Meta...**: Clean
- **Subm...**: 2/23/2016 10:21
- **Attach...**: View (0)
- **Series...**: Submitted
- **Comm...**: N/A
- **Publis...**: N/A
- **Published Date**: N/A
Important MRI Brain Imaging Parameters to remember for the required 3D acquisitions

The post gadolinium contrast-enhanced three-dimensional Imaging Sequence should use the smallest possible axial slice thickness not exceeding 1.5 mm.

Baseline MRI must be obtained ≤21 days prior to step 1 registration.
Important MRI Brain Imaging Parameters to remember for the required T2 FLAIR acquisitions

- Axial acquisition is required
- Utilizing your site’s standard FLAIR sequence is acceptable as long as it is acquired in the axial plane
- 3D T2 FLAIR acquisition may be substituted, again as long as the acquisition is reformatted in the axial plane
Thank you
Questions

MRI Technical Contacts:

Tammie L.S. Benzinger, MD, PhD
Modality Co-Chair/Radiology
benzingert@wustl.edu

Cyndi Price AS RT (R)(MR)(ARRT)
ACR Clinical Research Center Core Laboratory
cprice@acr.org / 215-940-8863
RT Quality Assurance
NRG CC001/CC003 Centralized QA

- **Credentialing**
  - Hippocampal contouring, IMRT planning
  - Biannual training workshops
  - NRG CC001: 108 physicians, 79 sites
  - NRG CC003: 61 physicians, 47 sites

- **Central Review**
  - Real-time pretreatment rapid review

http://www.rtog.org/CoreLab/ContouringAtlases/HippocampalSparing.aspx

Rationale for Central Quality Assurance

- Credentialing: >90% passed on first attempt
- Pre-treatment review: ed
  disqualification/unacceptable deviation rt 30% to 5%

Gondi V, et al. IJROBP 2015
Credentialed Logistics

- Cross-fertilizes between NRG CC001 and CC003
- Similar infrastructure to RTOG 0933
- Facility Questionnaire and Credentialing Status Inquiry Form
  - [http://irochouston.mdanderson.org](http://irochouston.mdanderson.org)
- Phantom Irradiation
- Benchmark Cases
  - Sites/MDs from RTOG 0933 grandfathered in for CC001/CC003
  - Sites/MDs who pass benchmark case for CC001 grandfathered in for CC003
  - Limit of 2 physicians/site
Central Review Process for NRG-CC001/CC003

MRI/CT fusion and hippocampal contours are acceptable.

- HA-WBRT treatment plan is acceptable
- HA-WBRT treatment plan is not acceptable
- HA-WBRT IMRT re-planning can be done on originally submitted contours

MRI/CT fusion and hippocampal contours are not acceptable.

- Second complete benchmark test is required:
  a) Treating physician must successfully complete hippocampal contouring benchmark case
  b) Institution must pass benchmark case for HA-WBRT treatment planning

Complete review of one case enrolled to be credentialed

NB: Second physician only has to pass the MRI/CT fusion and generation of hippocampal contours portion of the benchmark test.
Central Review of Accrued Patients

- Pre-tx rapid review of first case from each site/MD
  - Even if credentialing grandfathered in from RTOG 0933 or NRG CC001
  - If passes 1\textsuperscript{st} pre-treatment review, then “green-lighted” to enroll without further pre-treatment review; but all cases reviewed post-treatment and feedback provided if unacceptable deviations
  - If passed pre-treatment review for CC001, then “green-lighted” for CC003 and vice-versa
NRG CC001 & CC003 Submission of RT DICOM data via TRIAD

Denise Manfredi BS, RT(T)
IROC PHILA RT Director
How To Obtain a TRIAD Log In

- A physics or Dosimetrist at the location where the RT will be administered must be on the enrolling site Roster as a TRIAD SITE User. The Lead RA at the site would handle this step (section 8.4.1).
- The physicist or dosimetrist would need to obtain an CTEP IAM account if they do not already have one. (see section 8 of the protocol for details).
- The physicist or dosimetrist will need to install TRIAD on a computer that they will use to upload the data from the Treatment Planning System (TPS).* Some sites require a staff member with Administrative rights to do this install. More details can be found at this link http://www.rtog.org/CoreLab/TRIAD.aspx
Click on the TRIAD Icon to launch.

Select from the drop down
*Clinical Trials (NCI Oncology)*
Use your CTEP IAM username and password to log in. Click *I agree and logon*.

**NOTE:** Password expires every 90 days.
1. Click on Submission.
2. Find the trial in the dropdown
3. The next dropdown
   Select your site
   CTEP # site
   select the enrolling site from the dropdown
Then select to import from your computer or your PACS. Most sites move the data to a folder on their computer. Select either from a file or folder to browse for the data.

Find the folder on your desktop to import from. Click OK.
Click on the + to ensure you have the following CT, RT Dose, RT Structure, RT Plan (not all TPS can export the plan file).

Pre-study MRI (brain trials)

Then click Move to Submission Queue.
1. Click the check mark box
2. If you are submitting the benchmark for credentialing this is what it will look like
3. Click on anonymize & upload
1. Select Subject ID from drop down list (populated from Rave)
2. Select **RT Digital plan** as Time Point and **Other** as Time point for the Pre study MRI
3. Select Clinical Trial as Submission Type
4. For the **RT Digital plan** click the yellow Validation button for status of structure naming compliance with the protocol. A green ✔️ it passes. A Red ❌ it failed. View the validation, if it failed-do not continue. Make the corrections in your TPS and start over
5. If it Passed the validation. Click Anonymize and upload

After TRIAD submission, a DDSI form must be completed at the link below

https://www.rtog.org/CoreLab/TRIAD.aspx

Generic username: irocuser
Generic Password: submitddsi1
Resources

- [https://www.rtog.org/CoreLab/TRIAD.aspx](https://www.rtog.org/CoreLab/TRIAD.aspx)
- Instructions on installation and submission can be found at the link above. As well as the DDSI form
Frequently Asked Questions
Frequently Asked Questions

- Is thin-slice 3D MRI standard imaging sequence?
- Is MRI follow-up after PCI for small cell lung cancer recommended?
- Is consolidative thoracic RT for extensive-stage small cell lung cancer permitted on NRG CC003?
- Is the use of IMRT during WBRT or PCI covered by insurance?