Learning Objectives

Upon completion, participants should be able to:

• Understand advances in systemic therapy that can impact the management of brain metastases

• Describe the key differences in rates of recurrence and cognitive decline associated with stereotactic radiosurgery versus whole-brain radiation therapy in patients with brain metastases

• Describe the current uses and limitations of laser interstitial thermal therapy for intracranial metastatic disease
Advances in Systemic Therapy for the Management of Brain Metastases

April K.S. Salama, MD

Case #1

- A patient in his 70s with newly diagnosed metastatic melanoma
- Enrolled in clinical trial of ipilimumab/nivolumab

Photos courtesy of April Salama, MD. Please see full prescribing information for warnings, efficacy, risk, and safety.
Ipilimumab + Nivolumab in Melanoma Brain Metastases

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Global</th>
<th>Intracranial</th>
<th>Extracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>4 (5)</td>
<td>16 (21)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (48)</td>
<td>25 (33)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Progressive disease(^a)</td>
<td>18 (24)</td>
<td>18 (24)</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Not evaluable(^b)</td>
<td>13 (17)</td>
<td>12 (16)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>Objective response rate, % (95% CI)</td>
<td>53 (41-65)</td>
<td>55 (43-66)</td>
<td>49 (38-61)</td>
</tr>
<tr>
<td>Clinical benefit rate(^c), % (95% CI)</td>
<td>59 (47-70)</td>
<td>60 (48-71)</td>
<td>52 (40-64)</td>
</tr>
</tbody>
</table>

\(^a\)Confirmed and unconfirmed PD; \(^b\)Includes unconfirmed responses; \(^c\)Clinical benefit rate = CR + PR + SD ≥ 6 months.

Please see full prescribing information for warnings, efficacy, risk, and safety.

<table>
<thead>
<tr>
<th>Events/Patients</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>24/75 NR (7.5-NR)</td>
</tr>
<tr>
<td>Extracranial</td>
<td>15/75 NR (NR-NR)</td>
</tr>
<tr>
<td>Global</td>
<td>25/75 NR (6.5-NR)</td>
</tr>
</tbody>
</table>


The percentage of patients with PFS at 6 months is 67%.
Case #2

- A patient in her 30s was treated with ipilimumab/nivolumab
- New brain metastases; started on dabrafenib/trametinib

**COMBI-MB: Phase 2 Trial of Dabrafenib + Trametinib**

**Key eligibility criteria**
- Cutaneous melanoma metastatic to the brain
- BRAF V600D/E/K/R mutation positive
- ≤ 2 prior metastatic melanoma systemic treatments
- No prior BRAFi or MEKi
- Corticosteroids permitted; stable or decreasing dose only for cohorts A-C

**Primary endpoint:** intracranial response rate in cohort A

Secondary endpoints: intracranial response rate in cohorts B, C, and D; extracranial response and overall response rates; intracranial, extracranial, and overall DCRs; duration of intracranial response, extracranial response, and overall response; PFS; OS; and safety

- Investigator-assessed efficacy was confirmed by a BIRC. Data cutoff date: November 28, 2016.

Photos courtesy of April Salama, MD.

Please see full prescribing information for warnings, efficacy, risk, and safety.
COMBI-MB: Phase 2 Trial of Dabrafenib + Trametinib

- **Cohort A (n = 76)**
  - Intracranial ORR: 58%
  - Intracranial DCR: 78%

- **Cohort B (n = 16)**
  - Intracranial ORR: 56%
  - Intracranial DCR: 88%

- **Cohort C (n = 16)**
  - Intracranial ORR: 44%
  - Intracranial DCR: 75%

- **Cohort D (n = 17)**
  - Intracranial ORR: 59%
  - Intracranial DCR: 82%

*Investigator assessed; these results were supported by independent review. Davies MA, et al. J Clin Oncol. 2017;35(suppl; abstract 9506). Please see full prescribing information for warnings, efficacy, risk, and safety.

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Patient-Centered Approach to Management of Brain Metastases

- Multidisciplinary Care
- Preclinical Models
- Duke Brain Metastasis and Spine Center
- Access to Clinical Trials
- Bioinformatics, Biospecimen Repository

Advances in Radiation Oncology for the Management of Brain Metastases

John Kirkpatrick, MD, PhD

WBRT vs SRS

- **WBRT**
  - Pro: Treats whole brain ⇒ Gross and subclinical metastasis
  - Con: Treats whole brain ⇒ Degrades cognition, QOL

- **SRS**
  - Pro: Treats lesion only ⇒ Less toxicity ⇒ Retains cognition/QOL
  - Con: Treats lesion only ⇒ Higher rate of new metastasis
  - Pro: Treats lesion only ⇒ High dose to lesion (high local control)
  - Con: Limited by size/volume/number of lesions

Neurocognitive Effects of WBRT

- **WBRT**¹
  - 5/47 (11%) patients who received WBRT for single brain metastasis developed dementia
  - 0/15 patients treated with < 3 Gy/fx RT alone developed dementia
- **RTOG 0212/0214: SRCF following PCI**²
  - 410 received PCI, 173 observation only
  - Significant drop in SRCF at 6 and 12 months post-PCI (OR = 3.44, \( P < .0001 \); OR = 3.6, \( P < .0001 \))
  - Significant decline in HVLT-Recall at 6 and 12 months post-PCI (\( P = .002 \))
- “All experience some decline, a few show a large decline”³


RCTs of SRS Alone vs SRS + WBRT

- No significant difference in OS¹⁻³
  - Except SRS alone was superior in small MD Anderson study²
- WBRT lowers rates of distant brain metastases³
  - Approximately 15% vs 50% with SRS alone
- WBRT slightly lowers rate of local recurrence¹
  - “True” rate of local recurrence obscured by SRS-induced imaging changes
- Neurocognition better with SRS alone²,³
  - Approximately 20% vs 50% deterioration in delayed recall 3 months post-SRS

RCTs of Postoperative RT

- High rates of local and distant recurrence for surgery alone vs surgery + WBRT\(^1\)
- Lower rates of neurocognitive decline in postoperative SRS vs WBRT\(^2\)
  - 52% vs 85% 6 months post-WBRT; \(P < .00031\)
  - No significant change in OS
- Lower rates of local recurrence in postoperative SRS vs observation alone\(^3\)
  - 43% vs 72%; \(P = .015\)
  - No significant change in OS


Multiple Brain Metastases…
Alternatives to WBRT?

- SRS?\(^1\)
  - Technically feasible….Upper limit on volume/number?
- Hippocampal sparing via IMRT?\(^2\)
  - Improved neurocognition vs WBRT….Limitations, role?
- Pharmaceuticals\(^3\)
  - Memantine*, donepezil*, amphetamines: partial value only
- Neuroprotectants\(^4\)


*Off-label.

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Multiple Brain Metastases… Alternatives to WBRT?

JLGK0901 Prospective SRS Study¹
- 1,194 patients with 1-10 brain metastases
  - Total volume < 15 mL
  - Unique isocenter/lesion
- Treated with 20-22 Gy SRS
- SRS for 5-10 metastases not inferior to SRS for 2-4 metastases
  - New lesions 63% vs 69%
  - AE 9% in both groups
- SRS vs WBRT not tested


Single-Isocenter Multi-Target SRS Retrospective Study²
- 59 patients with 4 or more brain metastases
- Treated with SIMT SRS at Duke, 2013-2015
- Brain metastasis volume, not number, affects OS

LITT: A Minimally Invasive Tool for Intracranial Lesion Ablation

Peter E. Fecci, MD, PhD
What Is LITT?

- Minimally invasive (< 1-cm incision)
- Stereotactic introduction of catheter with laser diode into a lesion
- Robotic control of depth and directionality
- Conducted in intraoperative vs diagnostic MRI suite with “real-time” MRI thermography—“cook” the lesion from inside out
- Calculated zones of “kill” and “stun”
- Patients typically home next day

LITT: Key Points

- LITT is a minimally invasive alternative to open resection, not an alternative SRS
- LITT offers cytoreduction—the GOAL OF SURGERY
Brain Metastases—The LITT Fit:  
When You Might Choose LITT Over Open Resection

- Treatment failures / recurrences
  - 5%-15% of patients receiving SRT/SRS
  - No gold standard
  - Poor wound healing after radiation
  - Maximum SRT dose
- Radiation “necrosis”
  - Few viable options
  - 10%-15%
  - Dexamethasone side effects
- Lesions suboptimal for resection
  - Subjective
  - Deep lesions (eg, thalamus, basal ganglia)
- Fragile patients
  - Elderly
  - Low KPS


Please see full prescribing information for warnings, efficacy, risk, and safety.

Limitations: Pushing the Pause Button

Large and/or Near Brainstem  
Superficial  
Periventricular

Photos courtesy of Peter Fecsi, MD, PhD.
Barring These Limitations…

• If you can safely biopsy, then you can offer cytoreduction via LITT, the GOAL OF SURGERY

Example: “Threading the Needle” to a Basal Ganglia Metastasis

Photos courtesy of Peter Fecci, MD, PhD.
Leading Use of LITT: Radiation “Necrosis”/Recurrent Metastases

Photo courtesy of Peter Fecci, MD, PhD.

Key Points: Recurrent Metastases vs Radiation Effect

- LITT permits early diagnosis (via biopsy)
- LITT treats results of biopsy effectively; for recurrent disease, LITT offers cytoreduction…the GOAL OF SURGERY
- LITT is easier to perform on radiated lesions than open surgery and retains benefits for wound healing compared with craniotomy
- Treating patients’ lesions with laser can allow patients to discontinue steroids or bevacizumab earlier

Case #3: My First Case With LITT

- A patient in their 80s with a history of NSCLC; left frontal metastasis that had been resected and SRS twice; presented with right-sided weakness and aphasia

Remember:

- LITT provides a minimally invasive surgical alternative
- LITT can be safely performed on lesions in nearly all locations
- If you can biopsy, you can LITT
Contact Information

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Brain Metastases: Abbreviations and Acronyms

AE = adverse event
BIRC = blinded independent review committee
BL = baseline
BM = brain metastases
BRAFi = BRAF inhibitor
CR = complete response
DCR = disease control rate
ECOG = Eastern Cooperative Oncology Group
HVLT = Hopkins Verbal Learning Test
IMRT = intensity-modulated radiation therapy
IR = intracranial response
KPS = Karnofsky Performance Score
LITT = laser interstitial thermal therapy
MEKi = MEK inhibitor
NR = not reached
ORR = overall response rate
OS = overall survival
PCI = prophylactic cranial irradiation
PD = progressive disease
PFS = progression-free survival
PR = partial response
PS = Performance Status
QOL = quality of life
RCT = random controlled trial
RT = radiation therapy
RTOG = radiation therapy oncology group
SD = stable disease
SIMT = single-isocenter multi-target
SRCF = self-reported cognitive function
SRS = stereotactic radiosurgery
SRT = stereotactic radiation therapy
WBRT = whole-brain radiation therapy