Advances in the Management of Brain Metastases

Developed in collaboration

Med-IQ DukeHealth

Learning Objectives

Upon completion, participants should be able to:

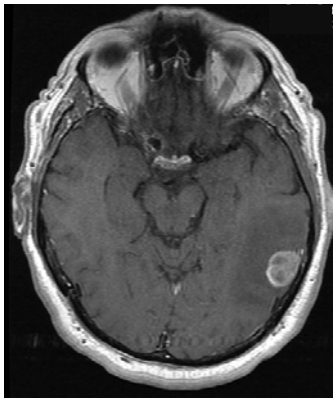
- Understand advances in systemic therapy that can impact the management of brain metastases
- Describe the key differences in rates of recurrence and cognitive decline associated with stereotactic radiosurgery versus whole-brain radiation therapy in patients with brain metastases
- Describe the current 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

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

[a]Confirmed and unconfirmed PD; [b]Includes unconfirmed responses; [c]Clinical benefit rate = CR + PR + SD ≥ 6 months.
Tawbi H, et al. *J Clin Oncol.* 2017;35(suppl; abstract 9507).
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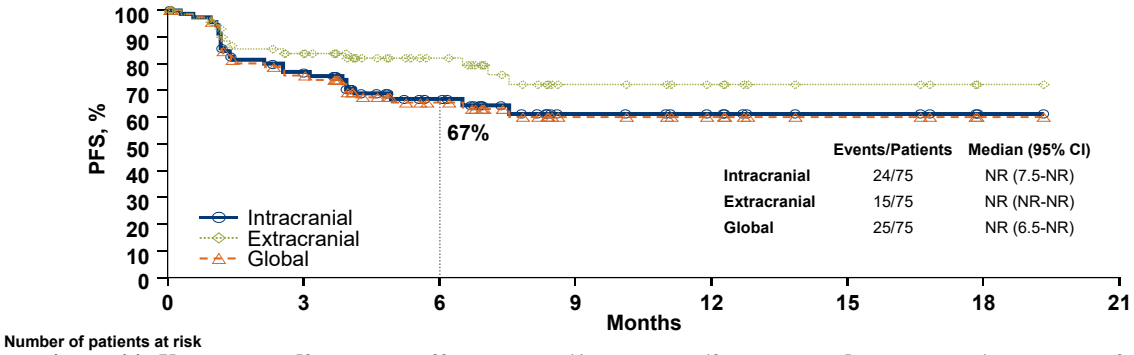
PFS



Number of patients at risk

Intracranial	75	50	30	14	10	5	1	0
Extracranial	75	52	31	14	10	5	1	0
Global	75	49	29	14	10	5	1	0

Tawbi H, et al. *J Clin Oncol.* 2017;35(suppl; abstract 9507).

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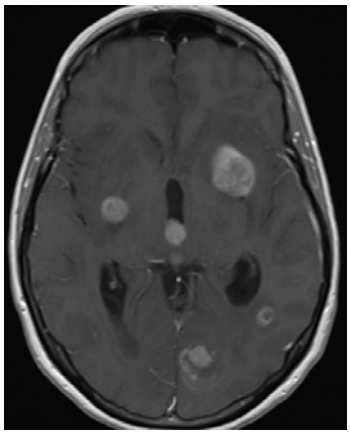
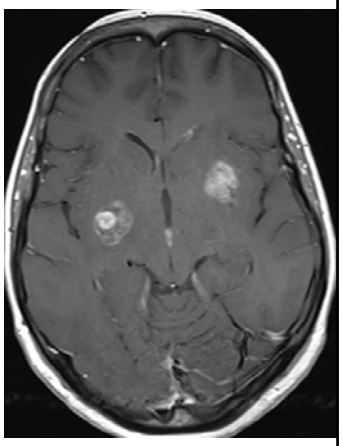
Case #2

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





Photos courtesy of April Salama, MD.
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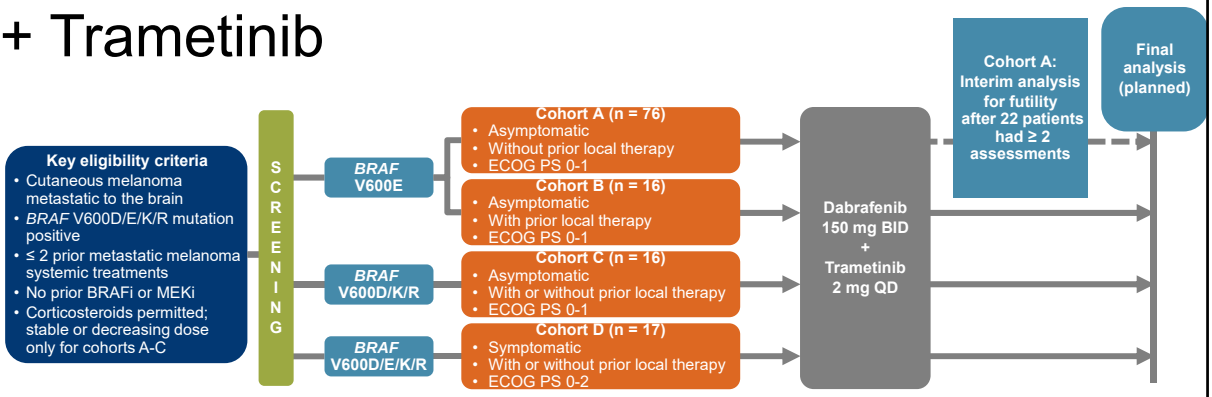
COMBI-MB: Phase 2 Trial of Dabrafenib + Trametinib



Primary endpoint: intracranial response rate in cohort A[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

[a]Null hypothesis: IR rate of ≤ 35% in cohort A (based on activity of dabrafenib monotherapy in the BREAK-MB trial; Long GV, et al. *Lancet Oncol.* 2012;13:1087-95). Investigator-assessed efficacy was confirmed by a BIRC. Data cutoff date: November 28, 2016.
Davies MA, et al. *J Clin Oncol.* 2017;35(suppl; abstract 9506).
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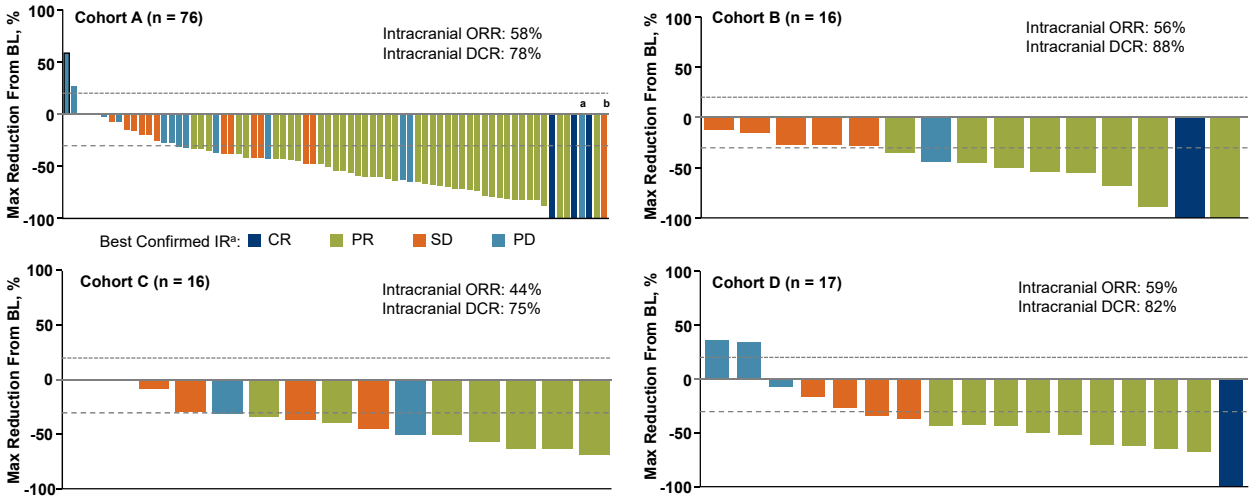

[a]Investigator assessed; these results were supported by independent review.
Davies MA, et al. *J Clin Oncol.* 2017;35(suppl; abstract 9506). Please see full prescribing information for warnings, efficacy, risk, and safety.

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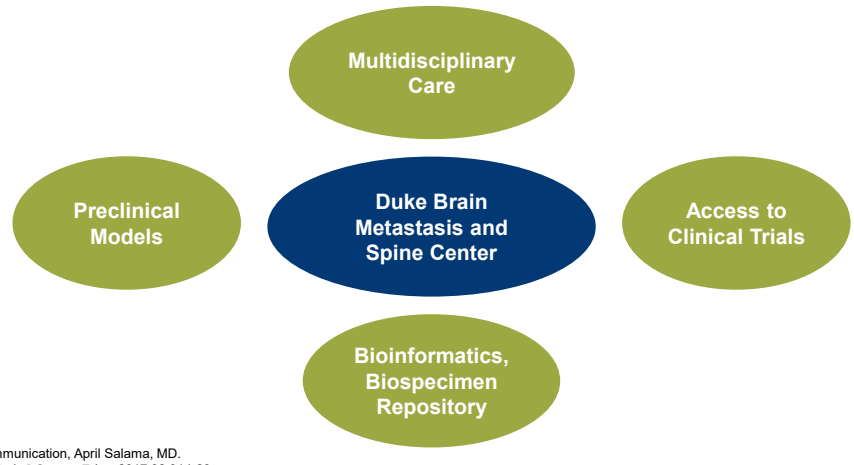
Patient-Centered Approach to Management of Brain Metastases



Personal communication, April Salama, MD.
Maqbool T, et al. *J Cancer Educ.* 2017;32:914-23.

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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

Tsao MN, et al. *Cochrane Database Syst Rev*. 2018;1:CD003869; Chao ST, et al. *Neurosurgery*. 2017. [Epub ahead of print]; Patil CG, et al. *Cochrane Database Syst Rev*. 2017;9:CD006121; Brown PD, et al. *JAMA*. 2016;316:401-9.

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]

1. DeAngelis LM, et al. *Neurology*. 1989;39:789-96; 2. Gondi V, et al. *Int J Radiat Oncol Bio Phys.* 2013;86:656-64; 3. Personal communication, John Kirkpatrick, MD, PhD.

RCTs of SRS Alone vs SRS + WBRT

- No significant difference in OS[1-3]
  - Except SRS alone was superior in small MD Anderson study[2]
- WBRT lowers rates of distant brain metastases[3]
  - Approximately 15% vs 50% with SRS alone
- WBRT slightly lowers rate of local recurrence[1]
  - "True" rate of local recurrence obscured by SRS-induced imaging changes
- Neurocognition better with SRS alone[2,3]
  - Approximately 20% vs 50% deterioration in delayed recall 3 months post-SRS

1. Aoyama H, et al. *JAMA*. 2006;295:2483-91; 2. Chang EL, et al. *Lancet Oncol.* 2009;10:1037-44; 3. Brown PD, et al. *JAMA*. 2016;316:401-9.

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

1. Patchell RA, et al. *JAMA*. 1998;280:1485-9; 2. Brown PD, et al. *Lancet Oncol*. 2017;18:1049-60; 3. Mahajan A, et al. *Lancet Oncol*. 2017;18:1040-8.

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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.
1. Yamamoto M, et al. *Int J Radiat Oncol Biol Phys*. 2017;99:31-40; 2. Limon D, et al. *Adv Radiat Oncol*. 2017;2:555-63;
3. Brown PD, et al. *Neuro Oncol*. 2013;15:1429-37; 4. McHaffie DR, et al. *J Neurooncol*. 2011;105:301-8.
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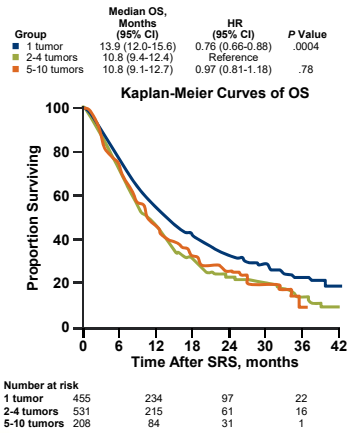
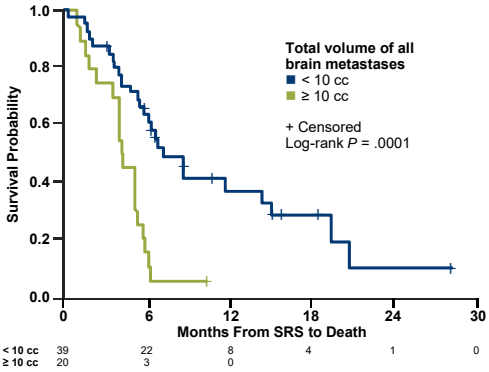
Multiple Brain Metastases… Alternatives to WBRT?



JLGK0901 Prospective SRS Study[1]

- 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 Study[2]

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

1. Yamamoto M, et al. *Int J Radiat Oncol Biol Phys.* 2017;99:31-40; 2. Limon D, et al. *Adv Radiat Oncol.* 2017;2:555-63.

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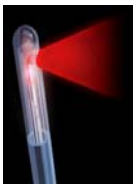
LITT:
A Minimally Invasive Tool for Intracranial Lesion Ablation

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



Ashraf O, et al. *World Neurosurg*. 2018;112:166-77; Lagan C, et al. *J Clin Neurosci*. 2017;36:20-6; Lee I, et al. *Neurosurgery*. 2016;79 Suppl 1:S24-34; Diaz R, et al. *Neurosurgery*. 2016;79 Suppl 1:S3-7; Sharma M, et al. *Expert Rev Neurother*. 2016;16:223-32.

LITT: Key Points

- LITT is a minimally invasive alternative to open resection, not an alternative SRS
- LITT offers cytoreduction—the GOAL OF SURGERY

Ashraf O, et al. *World Neurosurg*. 2018;112:166-77; Lagan C, et al. *J Clin Neurosci*. 2017;36:20-6; Lee I, et al. *Neurosurgery*. 2016;79 Suppl 1:S24-34; Diaz R, et al. *Neurosurgery*. 2016;79 Suppl 1:S3-7; Sharma M, et al. *Expert Rev Neurother*. 2016;16:223-32.

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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

Personal communication, Peter Fecci, MD, PhD, and John Kirkpatrick, MD, PhD; Ahluwalia M, et al. *J Neurosurg*. 2018;4:1-8; Rammo R, et al. *J Neurooncol*. 2018;138:609-17; Ashraf O, et al. *World Neurosurg*. 2018;112:166-77; Thomas JG, et al. *Neurosurg Focus*. 2016;41:E12; Wright J, et al. *Neurosurg Focus*. 2016;41:E14; Missios S, et al. *Neurosurg Focus*. 2015;38:E13.
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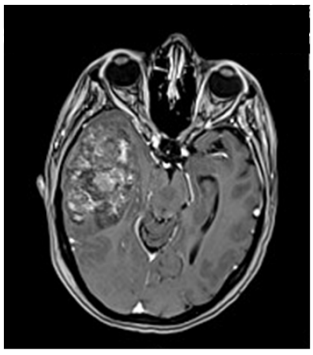
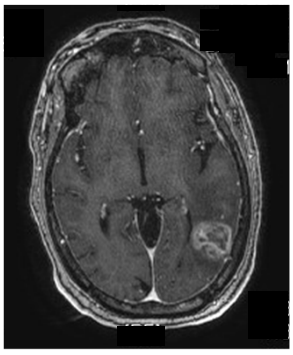
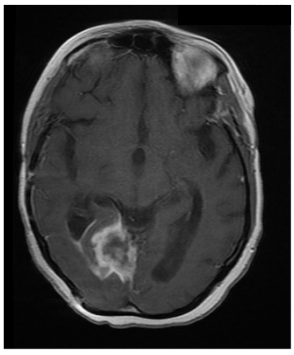
Limitations: Pushing the Pause Button



Large and/or Near Brainstem



Superficial



Periventricular

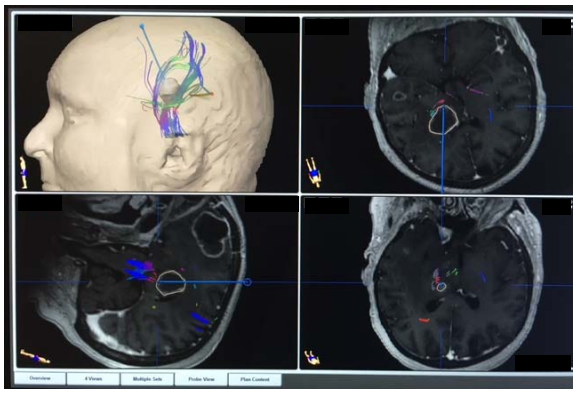
Photos courtesy of Peter Fecci, MD, PhD.

Barring These Limitations…

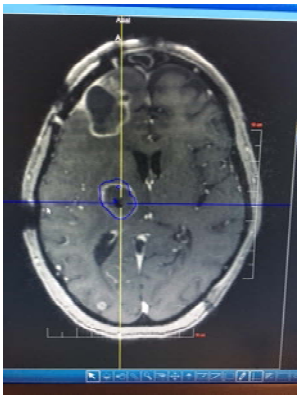
- If you can safely biopsy, then you can offer cytoreduction via LITT, the GOAL OF SURGERY

Personal communication, Peter Fecci, MD, PhD.

Example: "Threading the Needle" to a Basal Ganglia Metastasis



Planning



Postoperative "kill" zone

Photos courtesy of Peter Fecci, MD, PhD.

Leading Use of LITT: Radiation "Necrosis"/Recurrent Metastases

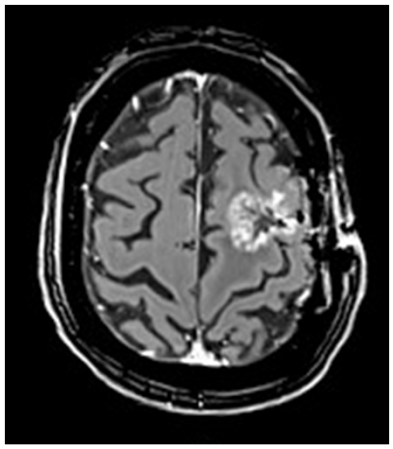


Photo courtesy of Peter Fecci, MD, PhD.

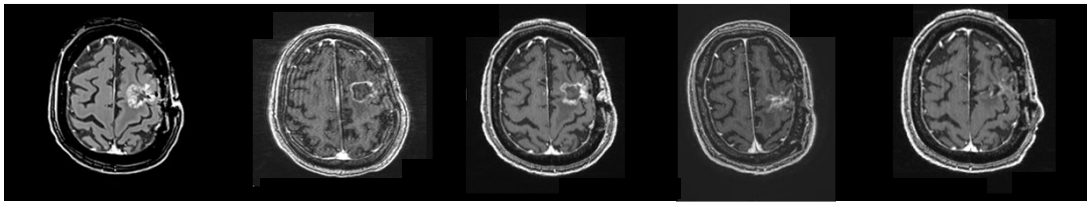
Key Points: Recurrent Metastases vs Radiation Effect

- 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

Personal communication, Peter Fecci, MD, PhD; Ahluwalia M, et al. *J Neurosurg*. 2018;4:1-8; Rammo R, et al. *J Neurooncol*. 2018;138:609-17; Ashraf O, et al. *World Neurosurg*. 2018;112:166-77; Thomas JG, et al. *Neurosurg Focus*. 2016;41:E12; Wright J, et al. *Neurosurg Focus*. 2016;41:E14; Missios S, et al. *Neurosurg Focus*. 2015;38:E13.

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



Pre-op	2 months	6 months	10 months	17 months
7/27/15	9/18/15	1/7/16	5/6/16	12/6/16

Photos courtesy of Peter Fecci, MD, PhD.

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

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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