Central Nervous System
Live SA-CME

Friday, March 2, 2018
10:00 a.m. – 11:30 a.m.
Social Q&A

Use your phone, tablet, or laptop to

➢ Submit questions to speakers and moderators
➢ Answer interactive questions / audience response polls

astro.org/RefresherSocialQA
Adult CNS Tumors

SA-CME

Lia M. Halasz, M.D.
Associate Professor and Residency Program Director
Departments of Radiation Oncology and Neurological Surgery
University of Washington
Faculty Disclosures

Faculty and Committee disclosures are also on the 2018 ASTRO Annual Refresher Course website.

<table>
<thead>
<tr>
<th>Name</th>
<th>Employment</th>
<th>Funding Sources</th>
<th>Ownership or Investments</th>
<th>Leadership</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lia Halasz, MD,</td>
<td>University of WA</td>
<td>Fred Hutch/University of Washington Cancer Consortium: Research Grants</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Disclosures

Clinical trial research funding from AbbVie
Employed by University of Washington
Learning Objectives

1. Articulate the treatment options for gliomas, skull base tumors, and brain metastases
2. Recognize areas where techniques are controversial or changing
3. Identify new trial results from recent years
New trial data from 2017-2018

Gliomas:
EORTC/NCIC elderly: 40 Gy in 15 with TMZ
EF-14: TTfields improve overall survival for GBM
CATNON interim report: Adjuvant TMZ for AA

Brain metastases:
NCCTG N107C/CEC.3: After resection, WBRT better local control but same OS as SRS
MDACC: SRS to resection bed improves local control

Meningiomas:
RTOG 0539: Good local control for atypical meningiomas treated with GTR + RT
Agenda

1. Anatomy and epidemiology
2. Glioma
3. Meningioma
4. Vestibular schwannoma
5. Brain metastases
Anatomy

- Meninges
- Skull
- Cerebrum
- Diencephalon
- Midbrain
- Pons
- Medulla oblongata
- Brain stem
- Convolution Sulcus
- Corpus callosum
- Transverse Fissure
- Cerebellum
- Spinal Cord
Anatomy

FRONTAL
TEMPORAL
PARIETAL
OCCIPITAL
CEREBELLUM

Anatomy

- Somatomotor
- Sensory speech area of Wernicke
- Reading comprehension
- Premotor
- Motor
- Productive speech area of Broca
- Acoustic area

Anatomy

Corpus callosum

Anterior commissure

Fornix

Need to follow contours over the corpus callosum

Niyazi et al. Rad Onc 2016
Anatomy

CN I
Olfactory tract

CN II
Optic chiasm and infundibulum

CN IV
Trochlear nerve

CN VII and VIII
Facial and vestibulocochlear nerves

CN III
Oculomotor nerve

CN V
Trigeminal nerve

CN VI
Abducens nerve

CN IX
Glossopharyngeal nerve

CN X
Vagus nerve

CN XI
Accessory nerve

CN XII
Hypoglosa nerve

Chiasm is above the sella, right under the brain
Epidemiology-primary brain tumors


ASTRO Annual Refresher Course • Fort Lauderdale Marriott Harbor Beach Resort & Spa • March 2-4, 2018 #REFRESHER18
Epidemiology—primary brain tumors

Malignant
N = 119,674
31.5%

Malignant Meningioma 0.5%
All Other Malignant 5.6%
All Other Malignant Glioma 10.6%
Glioblastoma 14.9%
Non-Malignant Glioma 1.1%
Non-Malignant Nerve Sheath Tumors 8.4%
Non-Malignant Pituitary Tumors 16.2%

Non-Malignant
N = 260,174
68.5%

Agenda

1. Anatomy and epidemiology
2. Glioma
3. Meningioma
4. Vestibular schwannoma
5. Brain metastases
Glioma classification

• Before 2016, WHO grade I-IV based on histology
• But, prognosis has always been unclear...

Glioma classification

- Molecular classification more accurate

Glioma mutations

- **Oligodendroglioma**
  - IDH mutated
  - 1p19q codeleted
- **Astrocytoma**
  - IDH mutated
  - 1p19q noncodeleted
- **LGG with IDH wild type**
  - Molecular GBM?
  - IDH wt astrocytoma provisional for now

Low Grade Glioma TCGA NEJM 372, 2015
# Glioma classification

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diffuse astrocytic and oligodendrogial gliomas</th>
<th>Diffuse astrocytic gliomas/glioblastomas</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>WHO grade II or grade III</td>
<td>WHO grade IV</td>
</tr>
<tr>
<td>IDH status</td>
<td>IDH-mutant</td>
<td>IDH-mutant</td>
</tr>
<tr>
<td>ATRX status</td>
<td>Nuclear ATRX retained</td>
<td>Nuclear ATRX retained*</td>
</tr>
<tr>
<td>1p/19q status</td>
<td>1p/19q-codeleted</td>
<td>1p/19q-non-codeleted</td>
</tr>
<tr>
<td>H3-K27M status</td>
<td>Oligodendroglia, IDH-mutant and 1p/19q-codeleted, WHO grade II or III</td>
<td>Astrocytoma, IDH-mutant, WHO grade II or III</td>
</tr>
<tr>
<td>Integrated diagnosis</td>
<td>Astrocytoma, IDH-mutant, WHO grade II or III</td>
<td>Glioblastoma, IDH-wild-type, WHO grade IV</td>
</tr>
<tr>
<td></td>
<td>Glioblastoma, IDH-mutant, WHO grade IV</td>
<td>Diffuse midline glioma, H3-K27M-mutant, WHO grade IV</td>
</tr>
</tbody>
</table>

Summary: Glioma classification

• Molecular classification
  • IDH mutant, 1p19q co-deleted = Oligodendroglioma
  • IDH mutant, 1p19q intact = Astrocytoma

• Provisional
  • IDH wt = Acts like GBM

• Histologic classification
  • IDH wt or IDH mutant = GBM

• Studies are based on old classification
  • We will discuss in context of new classification as well
Glioblastoma (GBM)
GBM

GBM Standard: EORTC/NCIC Trial

- Age <= 70
- Randomized 1:1
  - 60 Gy
  - 60 Gy/TMZ → TMZ
- Improved median survival
  - 12.1 → 14.6 months
  - P<0.001

MGMT methylated GBM does better

- DNA repair by O6-methylguanine methyltransferase
- Resistance to alkylating agents
- Prognostic and predictive significance

Hegi M, et al. JCO 2008
IDH mutated GBM does better

- IDH mutations are earliest detectable genetic alterations in precursor LGG
- Primary GBM = IDH wt
  - Secondary GBM = IDH mut
- Prognostic but not necessarily predictive

Zou P et al. PLOS One 2013
Sanson M et al. JCO 2009
RPA from RTOG 0525

Bell EH, et al. JAMA Oncology. 2017
GBM Standard: EORTC/NCIC Trial

- Age <= 70
- Randomized 1:1
  - 60 Gy
  - 60 Gy/TMZ → TMZ
- Improved median survival
  - 12.1 → 14.6 months
  - P<0.001

GBM: Recurs locally, but is actually diffuse

Single cell analysis utilizing IDH1 R132H antibody

Clinical trial strategies

- Radiation dose escalation in era of temzolomide (NRG BN-001)
- EGFR targeted
- Checkpoint inhibitors
- Vaccine studies
- CAR T Cells
- Electromagnetic fields
Tumor-Treating Fields

- KPS ≥ 70; median age 56
- Randomized 2:1 after 60 Gy/TMZ
  - Adjuvant TMZ + TTFields
  - Adjuvant TMZ
- Improved median survival (from time of randomization)
  - 16.0 → 20.9 months
  - P<0.001
- Toxicity
  - Skin toxicity in 52%

Stupp R et al. JAMA. 2017
Tumor-Treating Fields

Zhu P and Zhu J. Chin Clin Oncol 2017;6(4):41
Tumor-Treating Fields

Zhu P and Zhu J. *Chin Clin Oncol* 2017;6(4):41
Tumor-Treating Fields

Zhu P and Zhu J. *Chin Clin Oncol* 2017;6(4):41
GBM Standard

2005: Temozolomide


2015: Tumor treating fields

Stupp R et al. JAMA 2017
# GBM standard: Contouring guidelines

<table>
<thead>
<tr>
<th>RTOG</th>
<th>EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>46 Gy in 23 fractions</strong></td>
<td><strong>60 Gy in 30 fractions</strong></td>
</tr>
<tr>
<td>GTV1 = surgical cavity + residual enhancing tumor + surrounding edema</td>
<td>GTV = surgical resection cavity + residual enhancing tumor</td>
</tr>
<tr>
<td>CTV1 = GTV1 + 2 cm</td>
<td>CTV = GTV + 2 cm</td>
</tr>
<tr>
<td><strong>14 Gy in 7 fractions</strong></td>
<td></td>
</tr>
<tr>
<td>GTV2 = surgical cavity + residual enhancing tumor</td>
<td><em>In RTOG 0525 and CENTRIC trials, no difference in OS between EORTC and RTOG sites</em></td>
</tr>
<tr>
<td>CTV2 = GTV2 + 2 cm</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2
OAR definitions and dose limits in GBM patients - individual adaptation necessary according to the clinical situation. Most protocols allow ipsilateral cochlea to receive 60 Gy rather than compromise dose.

<table>
<thead>
<tr>
<th>OAR</th>
<th>If contouring on MRI always double check on CT in case of misalignment</th>
<th>Objective(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>The foramen magnum to the point where the optic tract passes lateral to the midbrain (this upper limit is arbitrary but easy to define and ensures consistency). Again, for consistency, the quadrigeminal (tectal) plate should be included.</td>
<td>$D \leq 54 \text{ Gy} \ [28]$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$1-10 \text{ cc} &lt; 59 \text{ Gy} \ (\text{periphery}) \ [28]$</td>
</tr>
<tr>
<td>Chiasm</td>
<td>Sits above and behind the anterior clinoids and runs backwards above the sella turcica. For consistency, the anterior and posterior 'limbs' should extend 5 mm to include the start of the optic nerves anteriorly and optic tracts posteriorly. The chiasm can sometimes only be seen on a single slice as it is about 3 mm thick in craniocaudal direction. It is often easiest to identify in the coronal plane</td>
<td>$D_{\text{max}} \leq 55 \text{ Gy} \ [28]$</td>
</tr>
<tr>
<td>Cochlea</td>
<td>Sit just anterior to the lateral aspect of the internal auditory canal. They are most easily identified on the CT bone windows as small cavities in the bone measuring 4–6 mm. Contour on 3 slices otherwise too small for dose calculation algorithms</td>
<td>Ideally one side mean &lt;45 Gy [33]</td>
</tr>
<tr>
<td>Eyes</td>
<td>The whole of the outside of the globe should be contoured to include sclera and cornea. The macula lies opposite the lens</td>
<td>Macula &lt;45 Gy [34]</td>
</tr>
<tr>
<td>Lacrimal glands</td>
<td>These can be difficult (sometimes impossible!) to see – but they lie on the superior and lateral aspect of the globe with the inferior border at the (axial) equator of the globe and wrap around superiorly about 30 degrees (i.e. face on - left eye from 1 o’clock and right eye 9 to 11 o’clock). They sit anterior to the (coronal) equator of the globe. Dose limits should not be used to compromise PTV dose</td>
<td>$D_{\text{max}} \leq 40 \text{ Gy} \ [21]$</td>
</tr>
<tr>
<td>Lens</td>
<td>Usually easy to see on the CT scan. However as cataracts are easily treatable the dose limits should never compromise PTV dose</td>
<td>Ideally &lt;6 Gy Max 10 Gy [21]</td>
</tr>
<tr>
<td>Optic nerves</td>
<td>From the back of the globe to the optic chiasm passing through the optic canal to enter the skull anterior and inferior to the anterior clinoid. To help identify the exact path through the orbit change to CT bone windows. Ensure they join up with optic chiasm. It may be useful to check the structure in the sagittal plane to ensure the outlined structure is not an extra-ocular muscle</td>
<td>$D_{\text{max}} \leq 54 \text{ Gy} \ [19]$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$D_{\text{max}} \leq 55 \text{ Gy} \ [28]$</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Within the sella turcica with chiasm lying superior and anterior to the stalk. As hypopituitarism is easily treatable the dose limits should never compromise PTV dose</td>
<td>$D_{\text{max}} \leq 50 \text{ Gy} \ [32]$</td>
</tr>
</tbody>
</table>
Timing of RT for GBM

- Metanalysis showed no evidence of delay of RT affecting OS
  - 19 studies
  - 5212 patients

Loureiro Rad Onc 118, 2016
Pseudoprogression

• One month post-chemoradiation
  • Half are bigger
  • 2/3 turn out to be pseudoprogression
  • If pseudoprogression, 2/3 have methylated MGMT
  • If early progression, 90% have unmethylated MGMT

Brandes et al. JCO 2008
Pseudoprogression

• pSPD associated with better survival (p=0.045)
• Unclear if psPD is a marker for better prognosis (mostly methylated patients) or leads to better prognosis

Brandes et al. JCO 2008
RANO: Response Assessment in Neuro-Oncology Criteria

• Call progression within 3 months of radiation therapy ONLY if:
  • New enhancement is beyond 80% isodose line
  • Unequivocal pathologic evidence of viable tumor

Wen PY et al. JCO 2010
## RANO after 3 months

<table>
<thead>
<tr>
<th>RANO Criteria</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 enhancing disease</strong></td>
<td>None</td>
<td>≥ 50%</td>
<td>&lt; 50% if ↓ but &lt; 25% if ↑</td>
<td>≥ 25% ↑</td>
</tr>
<tr>
<td><strong>T2/FLAIR</strong></td>
<td>Stable/improved</td>
<td>Stable/improved</td>
<td>Stable/improved</td>
<td>Stable/improved</td>
</tr>
<tr>
<td><strong>New lesion</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Present</td>
</tr>
<tr>
<td><strong>Corticosteroid use</strong></td>
<td>None</td>
<td>Stable or ↓</td>
<td>Stable or ↓</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Clinical status</strong></td>
<td>Stable/improved</td>
<td>Stable/improved</td>
<td>Stable/improved</td>
<td>Declined</td>
</tr>
</tbody>
</table>

Wen et al. JCO 2010; Okada et al. Lancet Oncol 2015

Elderly GBM: Canadian Study “Roa”

- Age > 60
- 40 Gy in 15 = 60 Gy in 30
  - 5.6 vs 5.1 months median survival
  - P=0.57
- No temozolomide

Roa et al. J of Clin Oncol 2004
Elderly GBM: IAEA ("Roa 2")

- Age ≥ 50/KPS 50-70
- Age ≥ 65 years/KPS > 70
- 25 Gy in 5 = 40 Gy in 15
  - 7.9 vs 6.4 months median survival
  - P=0.988
- No temozolomide
- 40% of patients had KPS 50-60

Roa et al. J of Clin Oncol 2015
## Performance status

<table>
<thead>
<tr>
<th>Karnofsky Scale</th>
<th>EORTC Zubrod scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no evidence of disease</td>
<td>Normal activity</td>
</tr>
<tr>
<td>Able to perform acitivity with only minor. symptoms</td>
<td>100</td>
</tr>
<tr>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>Normal activity with effort, some symptoms</td>
<td>Symptomatic and ambulatory</td>
</tr>
<tr>
<td>Able to care for self but unable to do normal activities</td>
<td>80</td>
</tr>
<tr>
<td>70</td>
<td>1</td>
</tr>
<tr>
<td>Requires occasional assistance, cares for most needs</td>
<td>Ambulatory &gt; 50% of time</td>
</tr>
<tr>
<td>Requires considerable assistance</td>
<td>60</td>
</tr>
<tr>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Disabled, requires special assistance</td>
<td>Ambulatory &lt;=50% of the time</td>
</tr>
<tr>
<td>Severely disabled</td>
<td>40</td>
</tr>
<tr>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td>Very sick, requires active supportive treatment</td>
<td>Ambulatory care needed</td>
</tr>
<tr>
<td>Moribund</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Bedridden</td>
<td></td>
</tr>
</tbody>
</table>
Elderly GBM: Nordic Trial

- Age > 60
- 60 Gy worse than 34 Gy/10 or TMZ alone
- Methylated MGMT associated with better survival for TMZ
  - Did not matter for RT

Elderly GBM: NOA-08

- Age > 65, KPS > 60
- TMZ = 60 Gy RT
  - 8.6 vs 9.6 mo median survival
- MGMT- benefited from RT not TMZ
- More toxicity with TMZ

Elderly GBM: CCTG/EORTC/TROG

- Age $\geq 65$, ECOG PS 0-2
- 40 Gy/TMZ $\rightarrow$ TMZ better than 40 Gy
  - 9.3 vs 7.6 mo median survival
  - $p<0.001$
- Benefit mostly for MGMT+ but also in MGMT-
  - ?whether methylation is most accurate test of MGMT

Summary: GBM

• <70 yo, good KPS
  • 60 Gy/TMZ → TMZ (Stupp 2005)
  • Consider TTFields (Stupp 2017)
  • Consider clinical trials (*NRG BN-001; ABT-414; PD1 inhibitors...*)

• ≥70 yo, good KPS
  • 40 Gy/TMZ → TMZ (Perry 2017)

• Poor KPS
  • Consider RT alone, TMZ alone, or best supportive care (*Wick 2012, Malstrom 2012, Roa 2004 and 2015*)

• Unknowns
  • Target volumes
  • Ongoing experimental agents
Question 1:
Which of the following factors is associated with longer survival for patients treated for glioblastoma?

a) Radiation treatment starting within 4 weeks of surgery
b) IDH1 mutation
c) Unmethylated MGMT
d) Older age
Question 2:
A right handed 46 year old man with a left posterior frontal glioblastoma is treated with 60 Gy involved field radiation therapy and temozolomide. On the 2 month post treatment imaging, there is increased size of enhancing tumor that is associated with increased surrounding edema and has mild worsening weakness of right upper extremity. What is the management of choice?

a) Changing from temozolomide to CCNU
b) Surgical resection
c) Starting dexamethasone and continuing with adjuvant temozolomide
d) Supportive care alone
Anaplastic astrocytoma (gr III nondeleted)
AA Gr III nondeleted: Interim CATNON

- 1:1:1:1 randomization
  - RT
  - RT/TMZ
  - RT → TMZ
  - RT/TMZ → TMZ
- Adjuvant TMZ improved OS
  - 5y OS 44% → 56%
- Unclear re: concurrent TMZ
- Benefit within 1 year (unlike PCV)

van den Bent MJ et al. Lancet. 2017
AA: NeoTMZ Nordic trial

- GBM and AA < 60 years old
  - Neoadj TMZ -> RT versus RT alone
  - After 2005 added concurrent TMZ
- Study closed early at 144 pts
  - 103 GBM, 41 AA
- Overall no benefit to neoTMZ
  - AA: 95.1 vs 35.2 mo (p=0.022)

Malmstrom A et al. Acta Oncologia. 2017
Anaplastic Oligodendroglioma (gr III codeleted)
### Anaplastic Oligodendroglioma (gr III codeleted)

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diffuse astrocytic and oligodendrogial gliomas WHO grade II or grade III</th>
<th>Diffuse astrocytic gliomas/glioblastomas WHO grade IV</th>
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<tbody>
<tr>
<td>IDH status</td>
<td>IDH-mutant</td>
<td>IDH-mutant</td>
</tr>
<tr>
<td>ATRX status</td>
<td>Nuclear ATRX retained</td>
<td>Nuclear ATRX lost</td>
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<tr>
<td>1p/19q status</td>
<td>1p/19q-codeleted</td>
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</tr>
<tr>
<td>H3-K27M status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Integrated diagnosis</td>
<td>Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade II or III</td>
<td>Astrocytoma, IDH-mutant, WHO grade II or III</td>
</tr>
</tbody>
</table>

Grade III AO/AOA: RTOG 9402

- AO/AOA
  - Includes both 1p19q codeleted and nondeleted
- PCV + RT versus RT
  - No difference in OS
    - ...but the curves split after 5 years

Cairncross G et al. JCO 2013
Grade III AO/AOA: RTOG 9402

**1p 19q codeletion**

- PCV + RT: Dead 28, Total 59
- RT: Dead 47, Total 67

**No deletion**

- PCV + RT: Dead 58, Total 76
- RT: Dead 53, Total 61

Median survival: 14.7 y vs 7.3 y

Cairncross G et al. JCO 2013
Grade III AO/AOA: RTOG 9402

IDH mut, 1p 19q codel

IDH mut, 1p 19q noncodel

IDH wt

14.7 vs 6.8 y  
5.5 vs 3.3 y  
1.3 vs 1.8 y

Cairncross et al. JCO 2014
Grade III AO: EORTC 26951

- AO/AOA
- RT+PCV versus RT
- Adjuvant PCV better tolerated than neoadjuvant PCV in RTOG 9402?

Can we use chemo alone?
NOA-04: Sequential single agents

Wick et al. JCO 2009
NOA-04: No difference in chemo vs RT

Fig. 2. Principal efficacy outcomes per treatment. Data of progression-free survival (PFS; panel A), time-to-treatment failure (TTF; panel B), and overall survival (OS; panel C) were analyzed by treatment arm.

Wick et al NeuroOnc 2016
NOA-04: Heterogeneous patient cohort

Oligo: 1p19q Codel, ATRX retained/p53wt
Astro: 1p19q intact, ATRX loss/p53mutant
~GBM: IDH wt

Wick et al NeuroOnc 2016
Can we use TMZ instead of PCV?

- For codeleted tumors
  - TMZ monotherapy worse than RT or PCV monotherapy
- Current CODEL trial: 1p/19q co-del anaplastic or high risk low grade glioma
  - RT/TMZ → TMZ
  - RT → PCV

Wick et al NeuroOnc 2016
# Low Grade Gliomas: Any grade II

<table>
<thead>
<tr>
<th>Histology</th>
<th>Diffuse astrocytic and oligodendrogial gliomas WHO grade II or grade III</th>
<th>Diffuse astrocytic gliomas/glioblastomas WHO grade IV</th>
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<td></td>
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<td>Astrocytoma, IDH-mutant, WHO grade II or III</td>
</tr>
</tbody>
</table>

Grade II: EORTC/RTOG 9802

- High risk: STR or age $\geq$ 40
- 43% oligodendroglioma
  - 31% mixed
  - 26% astrocytoma
- 54 Gy $\rightarrow$ PCV better than 54 Gy
  - Median survival 13.3y versus 7.8y
- Curves separate after 4 y

Buckner J et al. NEJM 2016
Grade II: EORTC/RTOG 9802

No 1p19q data...

Oligodendroglioma

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>50 48 48 45 43 43 41 39 36 34 32 28 20</td>
</tr>
<tr>
<td>RT alone</td>
<td>57 56 53 50 45 45 40 35 31 28 24 11</td>
</tr>
</tbody>
</table>

Oligoastrocytoma

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>39 34 33 29 27 24 21 20 18 16 14 10</td>
</tr>
<tr>
<td>RT alone</td>
<td>40 38 34 27 23 21 18 14 13 9 6 3</td>
</tr>
</tbody>
</table>

Astrocytoma

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years after Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>21 19 18 16 14 10 8 8 8 8 2</td>
</tr>
<tr>
<td>RT alone</td>
<td>22 20 18 16 14 10 8 8 8 8 2</td>
</tr>
</tbody>
</table>

Non significant, but only 65 patients

Buckner J et al. NEJM 2016
Grade II: EORTC/RTOG 9802

- Changed our approach to low grade glioma
  - The best prognosis patients (oligodendroglioma) benefited most from treatment
- Does not incorporate molecular categories
- Does not answer the question of whether we should observe after surgery
Can we use chemo alone?
Grade II: EORTC 22033-26033

- At least one high risk feature
  - Age>40, progressive disease, >5 cm, crossing midline, neuro symptoms
  - 40% oligo, 25% mixed, 35% astro
- 50.4 Gy = TMZ
  - Median PFS 39 months TMZ vs 46 months RT
- No molecular markers
- Given positive chemoRT trials, conclude no monotherapy

Hypermutated state after TMZ in LGG?

- Exome sequencing in 23 LGG tumors
  - At baseline and time of transformation to GBM
- 10 treated with TMZ monotherapy
  - 6 hypermutated when transformed
  - 97% of those were mutations characteristic of TMZ
  - Driver mutations different than non-TMZ patients

## LGG Contouring guidelines

<table>
<thead>
<tr>
<th>RTOG</th>
<th>EORTC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>54 Gy in 30 fractions</strong></td>
<td><strong>50.4 Gy in 28 fractions</strong></td>
</tr>
<tr>
<td>GTV1 = surgical cavity + T2/FLAIR</td>
<td>GTV = surgical cavity + T2/FLAIR</td>
</tr>
<tr>
<td>CTV1 = GTV1 + 1 cm</td>
<td>CTV = GTV + 1 cm</td>
</tr>
</tbody>
</table>

*CODEL trial incorporates boost to enhancing disease to 59.4 Gy*

Proton therapy?

- NRG BN-005:
- Grade II or III glioma stratified:
  - Baseline cognitive function
  - 1p19q
  - GTR/STR
- 54 Gy → TMZ
  - Randomized protons versus IMRT
  - Primary outcome is cognitive change
Summary:
Oligodendroglioma (1p19q codeleted)

- RT + PCV for grade III or high risk grade II (RTOG 9402, EORTC 26951, RTOG 9802)
  - No more oligoastrocytoma
- No more monotherapy (EORTC 22033-26033, NOA-04)
  - Though RT alone = Chemo alone, ChemoRT is better than RT alone
  - Thus, ChemoRT is best
- PCV versus TMZ question still outstanding
  - CODEL modified for any oligodendroglioma (grade II or III)
  - TMZ versus PCV
- Other unknowns
  - Who can be observed?
  - What are the long term side effects of combined treatment?
  - Should dose still be based on grade?
    - CODEL trial gives 50.4 Gy, and boost to 59.4 Gy for enhancing disease
Summary: Astrocytoma (1p19q retained)

• For WHO grade III: RT + Adjuvant TMZ (CATNON, Nordic)
  • Unknowns
    • Role of concurrent TMZ unclear
    • Does this apply to Grade II Astrocytomas? (more later)
    • Does IDH1 or IDH2 mutations predict for response?

• For high risk WHO grade II: RT + PCV (RTOG 9802) or TMZ
  • Unknowns
    • TMZ vs PCV
    • Who can be observed?
    • What is optimal therapy for IDH wt tumors?
<table>
<thead>
<tr>
<th>Histology/Grade</th>
<th>Molecular Type</th>
<th>My treatment</th>
<th>Median OS</th>
<th>Trial</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2 Astro</td>
<td>IDH mutant, 1p19q intact, ATRX loss, p53 mutant</td>
<td>54 Gy with CTV margin 1 cm $\rightarrow$ chemo</td>
<td>6+</td>
<td>RTOG 9802</td>
<td>PCV benefit for IDH mutants; unclear for grade II how TMZ compares to PCV</td>
</tr>
<tr>
<td>G3 Astro</td>
<td>59.4 Gy with CTV margin 1.5 cm/TMZ $\rightarrow$ TMZ</td>
<td>5+</td>
<td>RTOG 9802</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2 Oligo</td>
<td>IDH mutant, 1p19q codel, ATRX retained, p53 wt</td>
<td>54 Gy with CTV margin 1 cm $\rightarrow$ PCV</td>
<td>14+</td>
<td>RTOG 9802</td>
<td>Grade 2 and 3 are likely similar prognosis; unclear if TMZ will work as well</td>
</tr>
<tr>
<td>G3 Oligo</td>
<td>54 Gy with CTV margin 1.5 cm and boost enhancing disease to 59.4 Gy $\rightarrow$ PCV</td>
<td>14+</td>
<td>RTOG 9802  EORTC26951</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2/3 Provisional</td>
<td>IDH wt</td>
<td>59.4 Gy with CTV margin 1.5 cm/TMZ $\rightarrow$ TMZ</td>
<td>~2+</td>
<td>RTOG9402  RTOG 9802  RTOG 0424</td>
<td>Unclear how to treat these currently but no poor prognosis</td>
</tr>
<tr>
<td>G4</td>
<td>IDH wt or mutated</td>
<td>46 Gy with CTV margin 1.5 cm on FLAIR then 60 Gy with CTV margin 1.5 cm on enhancement/TMZ $\rightarrow$ TMZ (+TTF)</td>
<td>1-2</td>
<td>EORTC/NCIC EF-14</td>
<td>TTF often not adopted by patients; hypofractionated for elderly</td>
</tr>
</tbody>
</table>
# Anaplastic Gliomas (See GLIO-3/GLIO-4 for GBM)

## Adjuvant Treatment

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic oligodendroglioma (1p19q codeleted)</td>
<td>Fractionated external beam RT(^1) and neoadjuvant or adjuvant(^n) PCV chemotherapy (category 1)(^n) or Fractionated external beam RT(^1) with concurrent and adjuvant temozolomide chemotherapy(^n)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>Fractionated external beam RT(^1) with concurrent and adjuvant temozolomide chemotherapy(^n) or Fractionated external beam RT(^1) + neoadjuvant or adjuvant(^n) PCV or Fractionated external beam RT(^1)</td>
</tr>
<tr>
<td>Anaplastic gliomas(^a) Poor performance status (KPS &lt;60)</td>
<td>Fractionated external beam RT(^1) (hypofractionated [preferred] or standard) or PCV or temozolomide chemotherapy (category 2B)(^n) or Palliative/Best supportive care</td>
</tr>
</tbody>
</table>

---

**NCCN Guidelines**

[www.nccn.org](http://www.nccn.org)  
Accessed 2/18/18
EANO Guidelines

Question 3:
A 46 year old woman presented with seizure and has undergone resection of a left frontal anaplastic astrocytoma with 1p19q non-co-deletion and IDH1 mutation. What would be a recommended management strategy?

a) Observation with treatment on progression
b) Involved field radiation therapy alone
c) Involved field radiation therapy followed by tumor treating fields
d) Radiation therapy with concurrent temozolomide followed by adjuvant temozolomide
SA-CME

Question 4:

Recent randomized trials on low grade glioma have established that:

a) Observation with delayed radiation therapy after gross total resection decreases overall survival
b) Tumor treating fields improves overall survival by 2 months
c) Adding adjuvant chemotherapy after radiation therapy improves overall survival
d) Dose escalation to 59.4 Gy improves overall survival
Agenda

1. Anatomy and epidemiology
2. Glioma
3. Meningioma
4. Vestibular schwannoma
5. Brain metastases
Meningiomas
Meningioma Challenges

• No randomized data
  • Mostly retrospective, single institution
• Long follow up needed given slow growing nature
• Heterogeneous group of tumors
• Our therapies are associated with morbidity
  • Can cause iatrogenic death
## Resection: Simpson Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Recurrence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>GTR tumor, dural attachment, and bone plus stripping of 2-4 cm dura</td>
<td>0% at 5 y*</td>
</tr>
<tr>
<td>1</td>
<td>GTR tumor, dural attachment, abnormal bone</td>
<td>9%*</td>
</tr>
<tr>
<td>2</td>
<td>GTR tumor, coagulation of dural attachment</td>
<td>19%</td>
</tr>
<tr>
<td>3</td>
<td>GTR without resection or coagulation of dural attachment; extradural</td>
<td>29%</td>
</tr>
<tr>
<td></td>
<td>extension</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Partial resection of tumor</td>
<td>44%</td>
</tr>
<tr>
<td>5</td>
<td>Decompression +/- biopsy</td>
<td></td>
</tr>
</tbody>
</table>

25 year follow up after surgery

<table>
<thead>
<tr>
<th>Simpson Grade</th>
<th>10 years</th>
<th>25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-5 (13 p)</td>
<td>62% (8 p)</td>
<td>69% (8+1 p)</td>
</tr>
<tr>
<td>3 (12 p)</td>
<td>33% (4 p)</td>
<td>42% (4+1 p)</td>
</tr>
<tr>
<td>1-2 (24 p)</td>
<td>13% (3 p)</td>
<td>38% (3+6 p)</td>
</tr>
</tbody>
</table>

Table 2. Number of Patients With a Recurrence After 10 and 25 Years, According to Surgical Radicality

Meningiomas continue to recur

- 363 patients from MDACC
  - Regraded per WHO 2007
  - 74% grade I
  - 23% grade II
  - 3% grade III
- Only 8 had RT

Recurrent meningioma are harder to treat

Changes in disease free interval by # of recurrences for atypical meningioma

Meningioma by grade...

- Grade I or image defined: Observation versus surgery versus RT (SRS or fractionated)
  - Subtotal resection +/- RT
- Grade II: Gross total resection +/- RT
  - Subtotal resection + RT
- Grade III: Surgery + RT

- Traditionally based on retrospective data and institutional bias
- Two trials recently accrued
  - RTOG 0539
  - EORTC 22042–26042
## RTOG 0539: phase II study

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Grade</th>
<th>Surgery/Recurrence</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>I</td>
<td>GTR (Simpson I-III)</td>
<td>Observation</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>STR (Simpson IV-V)</td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>I</td>
<td>Recurrent</td>
<td>54 Gy to GTV + 1 cm (0.5 cm at natural barriers)</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>GTR</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>II</td>
<td>Recurrent or STR</td>
<td>54 Gy to GTV + 2 cm → 60 Gy to GTV + 1 cm</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>

*GTV includes tumor bed and any residual nodular enhancement*
Observation of incidental meningiomas

• 110 patients
  • 113 incidental meningiomas
• Mean age 66.8 y
• Mean follow up 46.9 mo
  • 15% volumetric change = growth
• Location matters

SRS for benign meningioma

• 4565 patients with 5300 tumors
  • 15 centers
• SRS to median dose 14 Gy
• Median 63 months
• Tumor control higher
  • Image defined vs grade 1
  • Female vs male
  • Sporadic vs multiple meningiomas
  • Skull base vs convexity
• Permanent morbidity 6.6% at last follow up

Regression (and progression) may take time

Transient progression may be seen

Risk of Radiation-Induced Tumors

- 1837 patients at Mayo, 11264 patient years
  - 1990-2009
- Risk of radiation-induced tumor after SRS
  - 0.0% at 15 y
- Risk of malignant transformation
  - 2.2% meningiomas
  - 0.3% vestibular schwannoma
  - 2.4% at 15 y, median 4.9 years
  - None for pituitary adenomas or glomus tumors

Pollock B et al. IJROBP 2017
## RTOG 0539: phase II study

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Grade</th>
<th>Surgery/Recurrence</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Observation</td>
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<td></td>
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<tr>
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<td>II</td>
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<td>III</td>
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</tr>
</tbody>
</table>

*GTV includes tumor bed and any residual nodular enhancement*
Historical context for RTOG 0539

Rogers et al. J Neurosurg 2017
Intermediate risk: RTOG 0539

- Grade II s/p GTR or recurrent grade I
  - Adjuvant RT 54 Gy
  - 3y PFS 93.8%
  - 3y OS 96%
- No grade 3+ AEs

Rogers et al. J Neurosurg 2017

FIG. 4. Progression-free survival, determined with progression and/or death as events. The 3-year PFS rate was 93.8% (95% CI 87.2%–100%).

<table>
<thead>
<tr>
<th>Category</th>
<th>Group II (n=51*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>η and (%) of Patients by Grade</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(13.7)</td>
</tr>
<tr>
<td>Dermatology/skin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(3.9)</td>
</tr>
<tr>
<td>Neurology</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>(13.7)</td>
</tr>
<tr>
<td>Ocular/visual</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>(11.8)</td>
</tr>
</tbody>
</table>

Adverse events were graded with CTCAE version 3.
Historical context for RTOG 0539

Rogers et al. J Neurosurg 2017
Current Trials: Atypical Meningioma

• NRG BN-003
  • Grade II GTR +/- 59.4 Gy RT
    • Protons or IMRT

• ROAM/EORTC 1308
  • Grade II GTR +/- 60 Gy RT

• Assess overall survival and late effects/QOL
## RTOG 0539: phase II study

<table>
<thead>
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<th>Treatment Details</th>
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<tr>
<td>High</td>
<td>III</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>

*GTV includes tumor bed and any residual nodular enhancement*
Molecular classification?

- DNA methylation-based classification
- Retrospective, multicenter
- 497 meningiomas

Sahm F et al. Lancet Oncol 2017
This may be why it is so hard to predict:

Histological subtype → Methylation class →

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>WHO Grade I</th>
<th>WHO Grade II</th>
<th>WHO Grade III</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN</td>
<td>TRANS</td>
<td>PSAM</td>
<td>CLEAR</td>
</tr>
<tr>
<td>TRANS</td>
<td>FIBRO</td>
<td>SECR</td>
<td>CHOR</td>
</tr>
<tr>
<td>FIBRO</td>
<td>PSAM</td>
<td>ANG</td>
<td>ATYP</td>
</tr>
<tr>
<td>PSAM</td>
<td>SECR</td>
<td>META</td>
<td></td>
</tr>
<tr>
<td>SECR</td>
<td>ANG</td>
<td>MICR</td>
<td></td>
</tr>
<tr>
<td>ANG</td>
<td>META</td>
<td></td>
<td>MC int-A</td>
</tr>
<tr>
<td>META</td>
<td>MICR</td>
<td></td>
<td>MC int-B</td>
</tr>
<tr>
<td>MICR</td>
<td></td>
<td></td>
<td>MC mal</td>
</tr>
</tbody>
</table>

Sahm F et al. Lancet Oncol 2017
Summary: Meningioma

• Much will change in the future with new trial and molecular data

<table>
<thead>
<tr>
<th>Grade</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Image defined</td>
<td>Observe</td>
</tr>
<tr>
<td>I after STR</td>
<td>Observe</td>
</tr>
<tr>
<td>II after GTR</td>
<td>Observe</td>
</tr>
<tr>
<td>II after STR</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td></td>
</tr>
</tbody>
</table>
Agenda

1. Anatomy and epidemiology
2. Glioma
3. Meningioma
4. *Vestibular schwannoma*
5. Brain metastases
Vestibular schwannoma

SRS 12-13 Gy
Vestibular schwannoma data

- Options:
  - Observation
  - Surgery
  - SRS
  - Hypofractionated SRT
  - Fractionated SRT

- No randomized trials
  - No uniform definition of local control, hearing preservation

Mansouri et al 2015
What outcomes matter?

- Tumor control
- Additional interventions needed
- Facial nerve presentation
- Balance
- Hearing preservation
- Patient satisfaction
- Cost
- Quality of life
Prospective (nonrandomized) trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Tumor Diameter</th>
<th>Procedure</th>
<th>Hearing Preservation</th>
<th>Facial Nerve Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollack et al</td>
<td>&lt; 3 cm</td>
<td>Surgery = 36</td>
<td>5% at last fup</td>
<td>69% at 1y</td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td>SRS = 46</td>
<td>63% at last fup</td>
<td>100% at 1y</td>
</tr>
<tr>
<td>Myrseth et al</td>
<td>&lt; 2.5 cm</td>
<td>Surgery = 28</td>
<td>0% at 2y</td>
<td>54% at 2y</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td>SRS = 63</td>
<td>68% at 2y</td>
<td>98% at 2y</td>
</tr>
<tr>
<td>Regis et al</td>
<td>Koos stage II &amp; III</td>
<td>Surgery = 110</td>
<td>5% at last fup</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>SRS=97</td>
<td>54% at last fup</td>
<td></td>
</tr>
</tbody>
</table>

*High-volume centers report hearing preservation rates 40-50%*

*Study by Myrseth et al did not use middle fossa aproach of CN VIII monitoring*
SRS/FSRT

- Systematic review
  - 19 large series with > 5 y follow up
  - New intervention needed


![Graph showing loss of tumor control (new intervention) over follow-up months for SRS and FSRT](image-url)
SRS/FSRT

• Systematic review
  • 14 large series with > 5 y follow up
  • Hearing deterioration

• Note: with 10 y follow up in some series, hearing deterioration worsens from 30% to 60%

Dose for vestibular schwannoma

• For SRS, initially higher doses were used
  • 1980s-early 1990s: median 16 Gy, up to 25 Gy with high CN V, VII injury
• For SRS, presently lower doses have comparable local control
  • 1990s-present: 12-13 Gy with local control > 90% (some 100%) at 10 years
  • CN V and VII complications < 5%
• Hypofractionated stereotactic radiation therapy
  • 20-25 Gy in 5 fractions
• Fractionated SRT
  • 50.4 Gy in 28 fractions
Treatment effect
Post-irradiation tumor expansion

- After radiation
  - 24% stable
  - 53% smaller
  - 23% larger
- Predictors of post-irradiation tumor expansion
  - Faster tumor growth rate
- Central clearing often noted

Niu et al. IJROBP 2014.
Summary: Vestibular Schwannoma

• Large tumors and those with vestibular symptoms = surgery
  • Small tumors = observation
  • Medium tumors = observation/SRS/SRT/surgery

• SRS to 12-13 Gy
  • Block dose to the cochlea if possible
  • Could consider hypofractionated SRT for intact hearing

• Multidisciplinary approach
  • Patient should know the options
  • Avoid specialist bias
Agenda

1. Anatomy and epidemiology
2. Glioma
3. Meningioma
4. Vestibular schwannoma
5. Brain metastases
Brain metastases
Treatment options for brain metastases

- Supportive care
  - Corticosteroids
- Whole brain radiation therapy (WBRT)
- Surgical resection
- Stereotactic radiosurgery (SRS)
- Systemic therapy
GPA: Graded Prognostic Assessment

Based on n=1960 RTOG trial patients

<table>
<thead>
<tr>
<th>Score</th>
<th>GPA: Graded Prognostic Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.5 - 4</td>
</tr>
<tr>
<td>0.5</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>1.5 - 2.5</td>
</tr>
<tr>
<td></td>
<td>0 - 1</td>
</tr>
</tbody>
</table>

Table 4. Graded Prognostic Assessment

<table>
<thead>
<tr>
<th>Age</th>
<th>Score</th>
<th>KPS</th>
<th>Score</th>
<th>No. of CNS metastases</th>
<th>Score</th>
<th>Extracranial metastases</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60</td>
<td>0</td>
<td>&lt;70</td>
<td>0.5</td>
<td>3</td>
<td>2-3</td>
<td>Present</td>
<td>None</td>
</tr>
<tr>
<td>50-59</td>
<td></td>
<td>70-80</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
<td>90-100</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GPA: Graded Prognostic Assessment

Spreduto P et al. IJROBP 2008
**Disease specific GPA**

**Table 1. Median Survival Time for Patients With Brain Metastases by DS-GPA Score**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Overall Survival Time (months)</th>
<th>No. of Patients</th>
<th>DS-GPA Score</th>
<th>Overall Survival Time (months)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median 95% CI</td>
<td>No. %</td>
<td>Median 95% CI</td>
<td>No. %</td>
<td>Median 95% CI</td>
</tr>
<tr>
<td>NSCLC</td>
<td>7.00 6.53 to 7.50</td>
<td>1,833</td>
<td>3.02 2.63 to 3.84</td>
<td>254 14</td>
<td>5.49 4.83 to 6.40</td>
</tr>
<tr>
<td>SCLC</td>
<td>4.90 4.30 to 6.20</td>
<td>281</td>
<td>2.79 1.83 to 3.12</td>
<td>65 23</td>
<td>4.90 4.04 to 6.51</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6.74 5.90 to 7.56</td>
<td>481</td>
<td>3.36 2.53 to 4.27</td>
<td>84 17</td>
<td>4.70 4.07 to 5.39</td>
</tr>
<tr>
<td>RCC</td>
<td>9.53 7.66 to 10.91</td>
<td>288</td>
<td>3.27 2.04 to 5.10</td>
<td>43 15</td>
<td>7.29 3.73 to 10.91</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>13.80 11.53 to 15.87</td>
<td>400</td>
<td>3.35 3.13 to 3.78</td>
<td>23 6</td>
<td>7.70 5.62 to 8.74</td>
</tr>
<tr>
<td>GI cancer</td>
<td>5.36 4.30 to 6.30</td>
<td>209</td>
<td>3.13 2.37 to 4.67</td>
<td>76 36</td>
<td>4.40 3.37 to 6.53</td>
</tr>
<tr>
<td>Other</td>
<td>6.37 5.22 to 7.48</td>
<td>450</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Total</td>
<td>7.16 6.88 to 7.52</td>
<td>3,940</td>
<td>3.10 2.83 to 3.46</td>
<td>546 16</td>
<td>5.40 4.90 to 5.89</td>
</tr>
</tbody>
</table>

Abbreviations: DS-GPA, diagnosis-specific Graded Prognostic Assessment; NSCLC, non–small-cell lung cancer; RCC, renal cell carcinoma; SCLC, small-cell lung cancer.

Spreduto P et al. JCO 2012
Brain metastases

• For many years, the standard was whole brain radiation therapy
  • As SRS became available in 1980s and early 1990s
  • Question: Does SRS add to WBRT?
Limited (1-3) brain metastases: WBRT +/- SRS

- RTOG 9508
- Randomized trial
- No difference in overall survival
  - Unless single metastasis

Andrews DW et al. Lancet 2004
Brain metastases

• Since SRS did not add to WBRT for many patients
  • Question: Can we avoid WBRT for patients with 1-3 brain metastases?
## Limited (1-4) brain metastases: SRS +/- WBRT

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median OS (months)</th>
<th>SRS</th>
<th>SRS + WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese Aoyama et al. JAMA 2006</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Local control (1 year)</td>
<td>73</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Distant control (1 year)</td>
<td>64</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Neurologic Death</td>
<td>19</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>MDACC Chang E et al. Lancet Oncol 2009</td>
<td>Cognitive Decline (HVLT at 4 months)</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td>Median OS</td>
<td>16</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Distant control (1 year)</td>
<td>45</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>EORTC 22952-26001 Kocher M et al. JCO 2011</td>
<td>Median OS</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Neurologic death</td>
<td>44</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Local failure (24 months)</td>
<td>31</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Distant failure (24 months)</td>
<td>48</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Alliance Brown PD et al. JAMA 2016</td>
<td>Cognitive decline (3 months)</td>
<td>64</td>
<td>92</td>
</tr>
<tr>
<td>Intracranial control (1 year)</td>
<td>51</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Median OS (1 year)</td>
<td>10</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
## WBRT improves local and distant control

<table>
<thead>
<tr>
<th>Trial</th>
<th>SRS</th>
<th>SRS + WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Japanese</strong> Aoyama et al. JAMA 2006</td>
<td>Median OS (months) 8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Local control (1 year) 73</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Distant control (1 year) 42</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Neurologic Death 19</td>
<td>23</td>
</tr>
<tr>
<td><strong>MDACC</strong> Chang E et al. Lancet Oncol 2009</td>
<td>Cognitive Decline (HVLT at 4 months) 24</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Median OS 16</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Distant control (1 year) 45</td>
<td>73</td>
</tr>
<tr>
<td><strong>EORTC 22952-26001</strong> Kocher M et al. JCO 2011</td>
<td>Median OS 11</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Neurologic death 44</td>
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<td>Intracranial control (1 year) 51</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Median OS (1 year) 10</td>
<td>7</td>
</tr>
</tbody>
</table>
WBRT improves local and distant brain control

- Example: EORTC 22952-26001
  - But, does it matter?
- WBRT does not change functional independence or survival
  - WBRT decreases neurological death

Kocher M et al JCO 2011
### WBRT does not improve overall survival

<table>
<thead>
<tr>
<th>Trial</th>
<th>SRS</th>
<th>SRS + WBRT</th>
</tr>
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<tbody>
<tr>
<td>Japanese Aoyama et al. JAMA 2006</td>
<td>Median OS (months)</td>
<td>8*</td>
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<td></td>
<td>Median OS (1 year)</td>
<td>10</td>
</tr>
</tbody>
</table>
WBRT does not improve overall survival

- No difference in overall survival
  - Aoyama - ?adequately powered
  - MDACC - Small numbers, but SRS group had improved OS
  - EORTC - Same OS
  - Alliance - No significant difference in OS
- But, are the trials adequately powered?
  - Meta-analysis by Sahgal A et al IJROBP 2017 suggests younger patients may have OS detriment from WBRT
## WBRT associated with worse neurocognition

<table>
<thead>
<tr>
<th>Trial</th>
<th>SRS</th>
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</thead>
<tbody>
<tr>
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</tr>
<tr>
<td></td>
<td>Median OS (1 year)</td>
<td>10</td>
</tr>
</tbody>
</table>
WBRT associated with worse neurocognition

• MDACC study showed decreased HVLT at 4 months
• Alliance trial showed > 1 SD in 1 of 6 tests at 3 months
  • Long term survivors also had worsened neurocognition
  • This is despite worse intracranial control and same overall survival

Brown PD et al. JAMA 2016
MDACC: Resection → SRS vs surveillance

• Randomized 132 patients with completely resected 1-3 brain metastases

• Technique
  • Surgical cavity + 1 mm circumferential margin
  • If close to dura, meningeal margin included
  • Surgical Tract not included
  • Cobalt based SRS

• Dose
  • ≤ 10 cc → 16 Gy
  • 10.1-15 cc → 14 Gy
  • >15 cc → 12 Gy
MDACC: Resection → SRS vs surveillance

Local control at 1 y
72% v 43%
p = 0.015

Overall survival
17 v 18 mo
p = 0.24

Freedom from distant brain recurrence at 1 y
42% v 33%
p = 0.35

*Only significant predictor of OS was stable versus progressive disease

*Only significant predictor of distant brain recurrence was number of mets

Mahajan A et al. Lancet Oncol 2017
## RT after surgery for limited metastases

<table>
<thead>
<tr>
<th>Randomized Trial</th>
<th>1 year local failure</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery alone</td>
<td>Surgery + RT</td>
<td></td>
</tr>
<tr>
<td>Patchell JAMA 1998</td>
<td>66%</td>
<td>20%</td>
<td>WBRT</td>
</tr>
<tr>
<td>Kocher JCO 2010</td>
<td>55%</td>
<td>27%</td>
<td>WBRT</td>
</tr>
<tr>
<td>Mahajan Lancet Oncol 2017</td>
<td>57%</td>
<td>28%</td>
<td>SRS</td>
</tr>
</tbody>
</table>

### Comments
- No radiographic evidence of necrosis
- <2.5 cm lesions -> 90% local control
- >? Hypofractionation for greater BED
NCCTG N107C/CEC.3: Resection → SRS vs WBRT

- Randomized 194 patients with resected brain metastasis
  - Did not have to be GTR
- Technique
  - Surgical cavity < 5 cm
  - Surgical cavity + 2 mm margin
- Dose
  - < 4.2 cc → 20 Gy
  - 4.2-7.9 cc → 18 Gy
  - 8.0-14.3 cc → 17 Gy
  - 14.4-19.9 cc → 15 Gy
  - 20.0-29.9 cc → 14 Gy
  - ≥30 cc → 12 Gy
NCCTG N107C/CEC.3: Resection → SRS vs WBRT

Cognitive-deterioration free survival
52.1% v 14.8% at 6 months
P=<=0.0001

Overall survival
12.2 v 11.6 mo
p=0.70

* >1 SD drop in at least 1 of 6 tests

Brown PD et al. Lancet Oncol 2017
**NCCTG N107C/CEC.3: SRS vs WBRT**

<table>
<thead>
<tr>
<th>At 1 year</th>
<th>Surgical bed control</th>
<th>Local control (unresected mets)</th>
<th>Distant brain control</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS</td>
<td>60.5%</td>
<td>61.8%</td>
<td>64.7%</td>
</tr>
<tr>
<td>WBRT</td>
<td>80.6%</td>
<td>87.1%</td>
<td>89.2%</td>
</tr>
<tr>
<td>P value</td>
<td>p=0.00068</td>
<td>p=0.00016</td>
<td>p=0.00045</td>
</tr>
</tbody>
</table>

Brown PD et al. Lancet Oncol 2017
NCCTG N107C/CEC.3: Resection → SRS vs WBRT

• Toxicities
  • Grade 3+: 12% SRS v 18% WBRT
  • SRS: fatigue, dyspnea, 4% grade 2+ CNS necrosis
  • WBRT: cognitive disturbance, hearing impairment, dehydration, nausea

• Notes
  • Local control determined by treating physician rather than central review
  • Radionecrosis is difficult to distinguish from recurrence sometimes
Resection bed contouring

- Consensus contouring paper
- 1-2 mm margin
- Extend along the dura 1-5 mm
- Surgical tract (?)

Is there any way to avoid neurocognitive effects of WBRT?

- WBRT dose?
- Memantine?
- Hippocampal sparing IMRT?
WBRT dose

• Cochrane review, Tsao, 2018
  • 10 published studies with 4056 participants
  • Altered WBRT dose fractionation compared to 30 Gy in 10 or 20 Gy in 5
  • No benefit overall survival, neurological function, or symptom control
RTOG 0614: WBRT + memantine vs placebo

- Randomized 508 patients with brain metastases
  - WBRT (37.5 Gy) + placebo
  - WBRT (37.5 Gy) + memantine x 6 months
- Primary endpoint: HVLT-R DR at 6 mo better with memantine
  - p = 0.059
- Overall survival: 7 vs 8 months (p=0.28)

Cognitive function failure = Failure in any of the tests

Brown Neuro-Onc 15, 2013
RTOG 0933: Hippocampal avoidance WBRT

• Single arm phase II study of 113 patients with HA-WBRT (30 Gy in 10)
  • Hippocampus+5mm: 100% < 9 Gy, Dmax <16 Gy
• Primary endpoint: Mean Relative Decline in HVLT-DR at 4 months compared to baseline
  • HA-WBRT: 7% decline in 0933
  • WBRT: 30% decline (historical control from Li et al, JCO 2007)
• NRG CC001 –WBRT + Memantine +/-Hippocampal Avoidance
  • WBRT 30Gy + Memantine x 6 m
  • HA-WBRT 30 Gy + Memantine x 6 m

Gondi JCO 32, 2014
Summary: Limited brain metastases

• WBRT
  • Improves local and distant control compared to SRS
  • Does not improve overall survival
  • Causes worse neurocognitive outcomes

• SRS
  • SRS alone is the best strategy for the majority of these patients
  • Improves local control when given postoperatively to tumor bed

• Strategies to reduce neurocognitive side effects ongoing
Multiple brain metastases

• Multiple series show that volume of disease is more important than number

<table>
<thead>
<tr>
<th></th>
<th>Multivariate Analysis for Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume of Metastases</td>
</tr>
<tr>
<td>Bhatnagar</td>
<td>p= 0.002</td>
</tr>
<tr>
<td>IJROBP2006</td>
<td></td>
</tr>
<tr>
<td>Likhacheva</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>IJROBP 2012</td>
<td></td>
</tr>
<tr>
<td>Baschnagel</td>
<td>p = 0.003</td>
</tr>
<tr>
<td>JNS 2013</td>
<td></td>
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<tr>
<td>Choi</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>IJROBP 2012</td>
<td></td>
</tr>
<tr>
<td>Shultz</td>
<td>P &lt;0.01</td>
</tr>
<tr>
<td>IJROBP 2015</td>
<td></td>
</tr>
</tbody>
</table>
Multiple metastases

- Japanese Observational Trial
  - 1194 patients
  - 1-10 brain metastases
  - \( \leq 15 \text{ mL cumulative volume} \)
- 2-4 mets versus 5-10 mets
  - 10.8 v 10.8 months, \( p=0.78 \)
- Only 9% had salvage WBRT
- Vast majority died of systemic disease progression

Yamamoto M et al. Lancet Oncol 2014
Summary: Multiple metastases

- Ongoing studies for SRS alone
- 2-15 mets at MDACC
  - Primary Outcome: Tumor control and cognitive function
- 4-19 mets at Netherlands
  - Primary Outcome: QOL

- In practice, I treat multiple metastases with SRS because the quality of life outcomes appear better and SRS is well tolerated
Can we omit radiation therapy for brain metastases?

• Supportive care alone should be considered
• Many new systemic therapies penetrate the blood brain barrier
QUARTZ trial

- 538 pts, unsuitable for SRS or surgery
  - Most received dexamethasone
- Supportive care +/- WBRT
- 9.2 weeks versus 8.5 weeks, p = 0.808
  - No difference QOL, steroid use
- WBRT associated with 4.7 QALY days
- Age < 60 had improved survival
  - Overall, 38% had KPS < 70

# Breast Cancer Brain Metastases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median intracranial response rate</th>
<th>Median OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib + capecitabine (HER-2)</td>
<td>66%</td>
<td>17</td>
<td>Bachelot T et al. Lancet Oncol 2013.</td>
</tr>
<tr>
<td>Lapatinib (HER-2)</td>
<td>6</td>
<td>6.4</td>
<td>Lin NU et al. Clin Cancer Res 2009</td>
</tr>
<tr>
<td>Neratinib (HER-2)</td>
<td>-</td>
<td>8.7</td>
<td>Freedman RA et al. JCO 2016.</td>
</tr>
</tbody>
</table>
# Melanoma Brain Metastases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median intracranial response rate</th>
<th>Median OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabrafenib (BRAF)</td>
<td>7-39%</td>
<td>4-8.2</td>
<td>Dummer R et al. Eur J Cancer 2014.</td>
</tr>
<tr>
<td>Ipilimumab (CTLA-4)</td>
<td>24%</td>
<td>7.0</td>
<td>Margolin K et al. Lancet Oncol 2012.</td>
</tr>
<tr>
<td>Pembrolizumab (PD1)</td>
<td>21%</td>
<td>9.9</td>
<td>Garon EB, et al. NEJM 2015</td>
</tr>
</tbody>
</table>
## Lung Cancer Brain Metastases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Median intracranial response rate</th>
<th>Median OS (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib (EGFR)</td>
<td>86 (with WBRT)</td>
<td>11.8</td>
<td>Welsh JW et al. JCO 2013</td>
</tr>
<tr>
<td>Afatinib (EGFR)</td>
<td>100</td>
<td>NR</td>
<td>Hoffknecht P et al. J Thorac Oncol 2015</td>
</tr>
<tr>
<td>Osimertinib (EGFR)</td>
<td>93</td>
<td>NR</td>
<td>Mok TS et al. NEJM 2017</td>
</tr>
<tr>
<td>Icotinib (EGFR)</td>
<td>67</td>
<td>NR</td>
<td>Wu YL et al. J Thorac Oncol. 2017</td>
</tr>
<tr>
<td>Ceritinib (ALK)</td>
<td>73</td>
<td>NR</td>
<td>DeCastro G et al. J Thorac Oncol. 2017</td>
</tr>
<tr>
<td>Crizotinib (ALK)</td>
<td>18-33</td>
<td>NR</td>
<td>Costa DB et al. JCO 2015.</td>
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<td>Alectinib (ALK)</td>
<td>64</td>
<td>NR</td>
<td>Gadgeel SM et al. JCO 2016, Lancet Oncol 2014</td>
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</tbody>
</table>
Can whole brain RT be held?

- EGFR mutated NSCLC
- At least three brain metastases
- Randomized Icotinib versus WBRT followed by chemotherapy

Yang JJ et al. Lancet Respiratory Medicine 2017
Can whole brain RT be held?

- EGFR mutated NSCLC
- Brain metastases
- Retrospective study

RTOG 0320: Adding Erlotinib to WBRT

- 1-3 brain metastases
- Arm 1: WBRT/SRS (13.4 mo)
- Arm 2: WBRT/SRS/TMZ (6.3 mo)
- Arm 3: WBRT/SRS/Erlotinib (6.1 mo)
- No statistically significant difference
  - More grade 4-5 toxicity in combined arms
  - (No EGFR testing)

Sperduto PW et al. IJROBP 2013.
Should we give radiation upfront?

- Retrospective
- 351 patients from 6 institutions
- EGFR mutant NSCLC with brain metastases
- Treated with SRS or WBRT and EGFR-TKI
- Propensity analysis confirmed findings

Magnuson WJ, et al. JCO 2017

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Follow-Up (months)</th>
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<tbody>
<tr>
<td></td>
<td>0</td>
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<tr>
<td>Upfront SRS</td>
<td>100</td>
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<tr>
<td>Upfront WBRT</td>
<td>120</td>
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<tr>
<td>Upfront EGFR-TKI</td>
<td>131</td>
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</table>
Immunotherapy/SRS: Timing matters

- Retrospective, Yale
- 75 patients treated with SRS and CTLA-4 and PD-1 inhibitors
- Concurrent = within 4 weeks of start or end of immunotherapy

Qian JM et al. J Neurooncology 2017

Lesion Volume Over Time

Concurrent treatment and anti-PD-1 has more effect
Immunotherapy/SRS: Timing matters

Qian JM et al. J Neurooncology 2017
Immunotherapy: More RT treatment effect?

- Retrospective, Dana Farber Cancer Institute
- 480 patients treated with SRS or SRT
- Symptomatic radiation necrosis
  - Pathology specimen
  - PET-CT
  - Serial MRIs

Martin AM, et al. JAMA Oncology 2018
Radiation treatment effect

Day 0  3 months  6 months
Radiation treatment effect

9 months
Treatment of radiation treatment effect

• Time
  • If asymptomatic, continue to follow
• Steroids
• Bevacizumab
  • In Levin et al IJROBP 2011, double blind randomized trial of 14 patients, all responded radiographically and clinically
• Surgical Resection
• Laser interstitial thermal therapy
Summary: Brain metastases

• For limited brain metastases, SRS alone allows for better neurocognitive outcomes
  • WBRT improves intracranial control but not overall survival

• For multiple brain metastases, trials are ongoing
  • However, volume of disease may be more predictive of survival than number of metastases
  • SRS alone is likely appropriate for many of these patients

• Still unclear whether RT should be given upfront or on progression for patients with targetable mutations

• Important to recognize treatment effect and treat appropriately
  • Often more radiation is not the answer
SA-CME

Question 5:
For patients with 1-3 brain metastases from lung cancer treated with stereotactic radiosurgery, which of the following statements is true regarding outcomes with the addition of whole brain radiation therapy?

a) Improves overall survival
b) Improves local control of the existing metastases
c) Improves functionally independent survival
d) Improves cognitive function
Summary

• For glioma classification, molecular markers are more prognostic than histology.
  • Meningioma may change similarly in the years ahead.

• Gliomas
  • GBM: TTF improves overall survival.
  • Elderly GBM: Hypofractionated RT + TMZ.
  • LGG: ChemoRT or observation (not monotherapy).
  • Grade III: ChemoRT

• Meningioma
  • Still controversial treatment decisions for grade I and II.
  • Ongoing trials to determine adjuvant RT for grade II, early data promising.

• Brain Metastases
  • WBRT does not improve OS for limited metastases and causes neurocognitive toxicity.
  • SRS for multiple metastases is less clear (but makes since). T
    • There are current trials and number of mets is not the most prognostic factor.
  • Increasing number of systemic therapies with CNS penetration creates controversy for timing of RT and perhaps increased treatment effect
Thank you