Disclosures

• Nektar Therapeutics – Consultant
• Stanford University – Employer
Learning Objectives

• Describe the clinical data underlying the current treatment of benign and malignant adult CNS tumors
• Review the data-based recommendations for chemotherapy, surgery and radiotherapy
• Understand the evolving molecular tests in CNS tumors which guide treatment recommendations
• Discuss the benefits and side effects of the multiple treatment options for brain metastases
Goals

• Highlight the data that forms the background of our treatment
• Highlight nuances of clinical treatment and practice
New Data in 2016-2017

General: WHO 2016 CNS Classification

Gliomas:
• RTOG 9802: Grade II Sequential RT-Chemo better OS than RT alone
• EORTC/NCIC Elderly GBM trial: 40 Gy in 15 with TMZ
• Wick NOA-04 Final Report: Grade III glioma monotherapy
• Baumert EORTC: Grade II glioma monotherapy
• Abstract: CODEL Interim report- TMZ monotherapy inferior
• Abstract: CATNON Interim report- Adjuvant TMZ better than no adjuvant TMZ

Brain Metastases:
• QUARTZ Final Report: For poor KPS, WBRT same as Hospice
• Brown NCCTG: WBRT + SRS worse for cognition than SRS alone
• Brown N107C Abstract: Post-op WBRT worse cognition than post-op SRS
Outline

- Glioma Molecular Overview
- Grade IV – Glioblastoma
- Grade II and III Gliomas – Oligos and Astros
- Brain Metastases
- Benign and Misc. Tumors
New WHO 2016 Classification of CNS Tumors

• ‘Formulating concept of how CNS tumor diagnoses are structured in the molecular era’
  – Most tumors now have a molecular underpinning, but not yet strictly a molecular diagnosis for all tumors
• Major restructuring of diffuse gliomas
  – Incorporating genetically defined entities
  – Notes: Now named Glioblastoma (no ‘multiforme’)
    Mixed Oligoastrocytomas ~don’t exist
• Major restructuring of medulloblastoma per genetics
• Solitary Fibrous Tumor/Hemangiopericytoma as one entity

Entering into a New Era: Integration of Molecular Subtype with Histology

Prognosis based on histology is unclear...

Entering into a New Era: Integration of Molecular Subtype with Histology

Oligodendroglioma

Astrocytoma, grade II or III

GBM, IDH-mutant

~GBM, IDH-wildtype

**Mutations in Gliomas**

<table>
<thead>
<tr>
<th>LGG with IDH Mutation and 1p/19q Codeletion</th>
<th>LGG with IDH Mutation and No 1p/19q Codeletion</th>
<th>LGG with Wild-Type IDH</th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RB1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIK3C2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NF1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDM4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDM2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDM1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDH1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFR3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFR2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FGFR1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDKN2A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDK6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDK4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATRX</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Low Grade Glioma TCGA NEJM 372, 2015**

This graph illustrates the distribution of specific alterations in genes across different subtypes of gliomas, highlighting the frequency of mutations in TP53, RB1, PTEN, PIK3R, and other genes. The graph shows a comparison between gliomas with IDH mutations and those with wild-type IDH, with a particular focus on the impact of 1p/19q codeletion on mutation rates.
Mutations in Gliomas

Summary:

Oligo: IDH mt, 1p19q Codeleted
Astro: IDH mt, 1p19q Not Codeleted
p53 mutated/ATRX loss

Oligo mutually exclusive from Astro
(~no longer have mixed oligoastros)

IDH-wildtype: ~molecular GBM

IDH wildtype astro is a 'provisional entry' in WHO 2016
(insufficient evidence to recognize as a distinct entity at this time)

Low Grade Glioma TCGA NEJM 372, 2015
Entering into a New Era: Integration of Molecular Subtype with Histology

Prognosis based on histology is unclear...

Entering into a New Era: Integration of Molecular Subtype with Histology

Prognosis based on molecular type is clear, trumping histology at times:
e.g., Histologic Low Grade, but molecularly and clinically more similar to GBM (IDH wt)

Molecular Type More Prognostic of OS than Histologic Grade

- For Oligos (IDH mut, co-deleted): grade II and III same OS
- For Astros (IDH mut, not codel): grade II and III similar OS
- More Unknowns: Unlike in TCGA, in Suzuki grade is prognostic for IDH wt
  - IDH wt tumors have ‘GBM-like’ mutations, but authors claim a distinct entity genetically
  - Therefore overall, still need more data

Integration of Molecular and Histologic Criteria

• At times, molecular type trumps histologic type:
  – A histologic oligo, but without 1p19q codeletion, is an astro
    • Confirm potential 1p19q test error by looking at p53, ATRX
  – A histologic grade II, but IDH-wildtype, is more similar to GBM

• At times, histology trumps molecular type:
  – An IDH-mutant (typically lower grade) with GBM histology, is GBM
Overall summary

• Future trials must include molecular subtyping
• More data needed to sort out if/how histologic grade II/III IDHwt glioma compares to a IDHwt GBM, as OS is same in some series (TCGA), but not in all (Suzuki)
Outline

• Glioma Molecular Overview

• Grade IV – Glioblastoma

• Grade II and III Gliomas – Oligos and Astros

• Brain Metastases

• Benign and Misc. Tumors
Glioma Histology

• Atypia
• Mitotic Figures
• Endothelial Proliferation
• Necrosis
## Surgery: GBM Extent of Resection

<table>
<thead>
<tr>
<th>Citation</th>
<th>Number of Patients</th>
<th>Extent of Resection (EOR)</th>
<th>OS (median)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacroix JNS 95, 2001</td>
<td>416</td>
<td>&lt;98%</td>
<td>8.8</td>
<td>Contributed to ‘all or none’ surgical philosophy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥98%</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Sanai JNS 115, 2011</td>
<td>500</td>
<td>&gt;78%</td>
<td>12.5</td>
<td>EOR as low as 78% still beneficial.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥80%</td>
<td>12.8</td>
<td>EOR significant even for 95 vs. 98 vs. 100% thresholds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;90%</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥100%</td>
<td>16.0</td>
<td></td>
</tr>
<tr>
<td>Chaichana NeuroOnc 16, 2014</td>
<td>259</td>
<td>≤70%</td>
<td>10.5</td>
<td>EOR as low as 70% still beneficial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;70%</td>
<td>14.4</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Retrospective data support a goal of maximum safe resection.
GBM Extent of Resection: Meta-analysis

- 41,117 patients
- 37 studies

Conclusion:
- If GTR, 61% more likely to be alive at 1 year
## HGG: Role for Radiotherapy

- **BTSG 69-01**
- **n=303 patients, high grade gliomas**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCNU alone</td>
<td>4.2</td>
</tr>
<tr>
<td>RT alone (50-60 Gy WBRT)</td>
<td>8.1</td>
</tr>
<tr>
<td>RT + BCNU</td>
<td>8.0</td>
</tr>
<tr>
<td>Supportive Care</td>
<td>3.2</td>
</tr>
</tbody>
</table>

First data for post-operative RT over supportive management

…and one of the only positive trials (other than BCNU wafers) for GBM until Stupp

**Walker JNS 49, 1978**
(One of the) Current Standards of Care:
EORTC 26981-22981/NCIC CE.3

- n=573 GBM
- Age 18 - 70y WHO 0-2

- RT 60 Gy
- RT 60 Gy + TMZ $\rightarrow$ TMZ x 6 months

- Temozolomide (TMZ)
  - 75mg/m2 QD during RT
  - 150-200mg/m2 d1-5 q28d x 6
  - PCP prophylaxis

Stupp, NEJM 352, 2005
Stupp 5 Year Update

Median OS: 12.1 vs. 14.6 months
2y OS: 11 vs. 27%

Figure 2: Kaplan-Meier estimates of overall survival by treatment group

Stupp Lancet 10, 2009
Stupp 5 Year Update

MGMT Hyper-Methylated
Median OS: 23.4 vs. 15.3

MGMT Not Hyper-Methylated
Median OS: 12.6 vs. 11.8 m
# Newly Diagnosed GBM: Role of Bevacizumab

<table>
<thead>
<tr>
<th>Citation:</th>
<th>Arms</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 0825 Gilbert NEJM 370, 2014</td>
<td>60 Gy + TMZ → TMZ</td>
<td>16.1</td>
</tr>
<tr>
<td></td>
<td>60 Gy + TMZ → TMZ + BEV</td>
<td>15.7 (NS)</td>
</tr>
<tr>
<td>AVAglio Chinot NEJM 370, 2014</td>
<td>60 Gy + TMZ → TMZ</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>60 Gy + TMZ → TMZ + BEV</td>
<td>16.8 (NS)</td>
</tr>
</tbody>
</table>

Bevacizumab does not improve OS for newly diagnosed GBM
First trials to prospectively show MGMT status as prognostic
Timing of Radiotherapy
Timing of Initiation of RT for GBM

• Meta-analysis:
  – 19 studies
  – 5212 patients

• Conclusion:
  No evidence of effect on OS by delay in RT in GBM

Loureiro Rad Onc 118, 2016
Radiotherapy Fields
RTOG RT Fields

• Initial to **46 Gy**:
  - T2 Edema + 2-3 cm

• Boost to **60 Gy**:
  - T1 post-Gad enhancement + 2-3 cm
EORTC/NCIC RT Fields

• Initial to 46 Gy:
  – T2 Edema + 2-3 cm

• Treat to 60 Gy (no cone down):
  – T1 post-Gad enhancement + 2-3 cm

• Most Recent EORTC trial:
  – T1 post-contrast + 1.5 cm CTV + 0.5 cm PTV
## ESTRO Contouring Guidelines

### Table 1
Guidelines for target delineation of glioblastoma, according to the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG).

<table>
<thead>
<tr>
<th>EORTC treatment volumes (EORTC 22981/22961, 26071/22072 (Centric), 26981–22981, and AVAglio trials)</th>
<th>RTOG treatment volumes (RTOG 0525, 0825, 0913, and AVAglio trials)</th>
</tr>
</thead>
</table>
| **Phase 1 (to 60 Gy in 30 fractions)**  
GTV = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans).  
CTV = GTV plus a margin of 2 cm<sup>*</sup>  
PTV = CTV plus a margin of 3–5 mm | **Phase 1 (to 46 Gy in 23 fractions)**  
GTV1 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans).  
CTV1 = GTV1 plus a margin of 2 cm (if no surrounding oedema is present, the CTV is the contrast enhancing tumour plus 2.5 cm.  
PTV1 = CTV1 plus a margin of 3–5 mm  
**Phase 2 (14 Gy boost in 7 fractions)**  
GTV2 = surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans)  
CTV2 = GTV2 plus a margin of 2 cm  
PTV2 = CTV2 plus a margin of 3–5 mm |

GTV = gross tumour volume; CTV = clinical target volumes; PTV = planning target volume.  
MRI = magnetic resonance imaging.  
<sup>*</sup> Margins up to 3 cm were allowed in 22981/22961 trial, and 1.5 cm in 26981–22981 trial.
Audience Question – Show of Hands

In planning radiotherapy volumes for GBM, I typically use:

1. 46 Gy to Edema + 14 Gy Cone Down = 60 Gy (RTOG)
2. 60 Gy to Cavity/Tumor (No Edema) = 60 Gy (EORTC)
3. Different Volume to 60 Gy
4. Different Dose other than 60 Gy
5. None of the above
In planning radiotherapy volumes for GBM, I typically use:

Standard of Care:
Dose – 60 Gy
Volume – no standard
Justification for EORTC fields (no edema):

- Retrospective studies:
  - Larger volume of brain treated, but no difference in patterns of failure with smaller fields
    - Minniti  Rad Onc, 2010
    - Chang    IJROBP 68, 2007

- Prospective data (but not the primary endpoint)
  - RTOG 0525\(^1\) and CENTRIC\(^2\):
    - No difference in OS between EORTC and RTOG sites

1. Gilbert JCO 31, 2013  
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] \n( 1-10 \text{ cc} &lt; 59 \text{ Gy (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 cranio-caudal plane. It is often easiest to identify in the coronal plane.</td>
<td>( D_{\text{max}} &lt; 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 \text{ 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 \text{ 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 to 3 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}} &lt; 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 \text{ 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] \n( D_{\text{max}} &lt; 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}} &lt; 50 \text{ Gy} ) [32]</td>
</tr>
</tbody>
</table>
XRT Fields

• Notes:
  – CTV is an anatomic concept, therefore can decrease CTV margin in areas where glioma cannot go
    • e.g., shave at tentorium, bone, falx (but not at falx near corpus callosum)
  – PTV is a geometric concept and is based on your machine, image fusion, intra- and inter-fraction movement, etc. Therefore no shaving of PTV
Contouring Example

CTV trimmed at falx

CTV not trimmed where falx stops at corpus callosum

Niyazi Rad Onc 118, 2016
Be Careful When Trimming CTV...
Be Careful When Trimming CTV...

Be aware of the falx/corpus callosum junction. Perhaps best seen on the coronal.
Be Careful When Trimming CTV...
Permanent Alopecia-Sparing VMAT

- Set ‘Skin’ as ‘Body’-4 mm and keep Dmax <40 Gy
- I hardly ever see permanent alopecia in follow-up anymore

Plan **without** constraint on ‘Skin’
Skin Dmax 50 Gy

Plan **with** constraint on ‘Skin’
Skin Dmax 40 Gy
Radiotherapy Dose
BTSG - Dose Response
retrospective from 66-01, 69-01, 72-01

<table>
<thead>
<tr>
<th>Dose (Gy WBRT)</th>
<th>Median OS (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>50</td>
<td>28</td>
</tr>
<tr>
<td>55</td>
<td>36</td>
</tr>
<tr>
<td>60</td>
<td>42</td>
</tr>
</tbody>
</table>

Walker IJROBP 5, 1979
RTOG 93-05: ChemoRT +/- SRS Boost

- \( n = 203 \) GBM (<40cc)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 Gy + BCNU</td>
<td>13.6</td>
</tr>
<tr>
<td>60 Gy + BCNU + upfront SRS</td>
<td>13.5</td>
</tr>
<tr>
<td>SRS per RTOG 90-05:</td>
<td></td>
</tr>
<tr>
<td>- 0-2cm 24 Gy, 2-3cm 18 Gy, 3-4cm 15 Gy</td>
<td></td>
</tr>
<tr>
<td>No benefit to SRS in newly diagnosed GBM</td>
<td></td>
</tr>
</tbody>
</table>

Souhami IJROBP 60, 2004
NRG-BN001

RANDOMIZED PHASE II TRIAL OF HYPOFRACTIONATED DOSE-ESCALATED PHOTON IMRT OR PROTON BEAM THERAPY VERSUS CONVENTIONAL PHOTON IRRADIATION WITH CONCOMITANT AND ADJUVANT TEMOZOLOMIDE IN PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

Arm A1: Reference Arm
Photon irradiation using 3DCRT or IMRT: 46 Gy in 23 fractions followed by a sequential boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

Arm B: Experimental Arm
Photon dose-intensified irradiation using IMRT: 50 Gy in 30 fractions with a simultaneous integrated boost to 75 Gy in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

Arm A2: Reference Arm
Photon irradiation using 3DCRT or IMRT: 46 Gy in 23 fractions followed by a sequential boost for an additional 7 fractions to 60 Gy
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

Arm C: Experimental Arm
Proton dose-intensified irradiation using passive scattered, uniform scanning beam, PBS or IMPT: 50 Gy(RBE) in 30 fractions with a simultaneous integrated boost to 75 Gy(RBE) in 30 fractions.
Plus
Concomitant temozolomide

4 weeks after completion of chemoradiation:
Adjuvant temozolomide x 6-12 cycles

*Randomization is 1:2 in favor of the experimental arm.
Post-ChemoRT Follow-up

• MRI at 1 month, then every 2 months
Post-ChemoRT Pseudoprogression (psPD)

- At the 1\textsuperscript{st} MRI at 1 month:
  - $\frac{1}{2}$ bigger
  - of those bigger – 2/3 are psPD
  - If psPD: 2/3 Me’d MGMT
  - If early progression: 90% un-Me MGMT

Brandes JCO 26, 2008
MGMT Methylated: More Pseudoprogession

Table 2. Effects of MGMT Promoter Methylation Status and First MRI Findings

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT promoter status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>11.7</td>
<td>20.7</td>
</tr>
<tr>
<td>Methylated</td>
<td>21.9*</td>
<td>43.6*</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>9.2</td>
<td>16.8</td>
</tr>
<tr>
<td>MRI findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>psPD</td>
<td>20.7*</td>
<td>38*</td>
</tr>
<tr>
<td>ePD</td>
<td>5.7</td>
<td>10.2</td>
</tr>
<tr>
<td>No PD images</td>
<td>11.4</td>
<td>20.2</td>
</tr>
</tbody>
</table>

Abbreviations: MGMT, O6-methylguanine–DNA methyltransferase; TTP, time to disease progression; OS, overall survival; psPD, pseudoprogession; ePD, early disease progression; PD, disease progression. *P = significant

Fig 3. Overall survival: blue line, patients with pseudoprogession; gray line, patients with early disease progression; yellow line, patients with neither pseudoprogession nor early disease progression.
MGMT and Patterns of Failure

• n=95
  – MGMT methylated: 34%

• Failure outside of field*
  – MGMT un-methylated: 15%
  – MGMT methylated: 40%

• Time to Progression:
  – In-field 9m
  – Out of field 15m

• *Historically – only ~15% out of field failures

Brandes JCO 27, 2009
Pseudo-progression

Prior to RT/TMZ 1 month 3 months 5 months
Response Assessment in Neuro-Oncology (RANO) Criteria

- Can call progression <3 months after radiotherapy ONLY if:
  - New enhancement beyond 80% Isodose line
  - Unequivocal pathologic evidence of viable tumor

Table 2. Criteria for Determining First Progression Depending on Time From Initial Chemoradiotherapy

<table>
<thead>
<tr>
<th>First Progression</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive disease &lt; 12 weeks after completion of chemoradiotherapy</td>
<td>Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or &gt;80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., &gt;70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.</td>
</tr>
</tbody>
</table>

Progressive disease ≥ 12 weeks after chemoradiotherapy completion

1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids.
2. Increase by ≥25% in the sum of the products of perpendicular diameters between the first postradiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids.
3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence.
4. For patients receiving antiangiogenic therapy, significant increase in T2/FLAIR nonenhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

Abbreviation: FLAIR, fluid-attenuated inversion recovery.

Wen JCO 28, 2010
GBM in Those with Advanced Age or Lower KPS
## GBM in the ‘Elderly’

<table>
<thead>
<tr>
<th>Citation</th>
<th>Arms</th>
<th>Median OS (months)</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keime-Guibert NEJM 356, 2007</td>
<td>No RT</td>
<td>4.3</td>
<td>RT better than supportive care</td>
</tr>
<tr>
<td></td>
<td>50.4 Gy</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Roa JCO 22, 2004</td>
<td>60 Gy in 30 frx</td>
<td>5.1</td>
<td>Short course no different than long course</td>
</tr>
<tr>
<td></td>
<td>40 Gy in 15 frx</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Wick NOA-08 Lancet 2012</td>
<td>60 Gy in 30 frx</td>
<td>9.6</td>
<td>TMZ is non-inferior to 60 Gy RT</td>
</tr>
<tr>
<td></td>
<td>TMZ 7 days in 14</td>
<td>8.6</td>
<td>EFS for MGMT Me’d: TMZ better (8.4 vs. 4.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EFS for MGMT not Me’d: RT better (4.6 vs. 3.3)</td>
</tr>
<tr>
<td>Malmstrom Lancet 2012</td>
<td>60 Gy in 30 frx</td>
<td>6.0</td>
<td>60 Gy in 30 <strong>worse</strong> than 34 Gy in 10</td>
</tr>
<tr>
<td></td>
<td>34 Gy in 10 frx</td>
<td>7.5</td>
<td>34 Gy in 10 not different than TMZ</td>
</tr>
<tr>
<td></td>
<td>TMZ 5 days in 28</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>Roa IAEA JCO 33, 2015</td>
<td>40 Gy in 15 frx</td>
<td>6.4</td>
<td>25 Gy in 5 non-inferior to 40 Gy in 15 for poor KPS</td>
</tr>
<tr>
<td></td>
<td>25 Gy in 5 frx</td>
<td>7.9</td>
<td></td>
</tr>
</tbody>
</table>
EORTC 26062-22061 / NCIC CE.6 / TROG 08.02: Hypo-fractionated RT + TMZ in ‘Elderly’

- n=562, >65 yo, ECOG 0-2
- Exclusion: Candidates for 60 Gy + TMZ

<table>
<thead>
<tr>
<th></th>
<th>mOS</th>
<th>MGMT +</th>
<th>MGMT -</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT 40 Gy (2.67 Gy x 15) + TMZ → TMZ</td>
<td>9.3</td>
<td>13.5</td>
<td>10.0</td>
</tr>
<tr>
<td>RT 40 Gy (2.67 Gy x 15)</td>
<td>7.6</td>
<td>7.7</td>
<td>7.9</td>
</tr>
</tbody>
</table>

p<0.001  p<0.001  p=0.055

Conclusion:

TMZ improves OS in all elderly GBM, more so in MGMT methylated
Even MGMT un-methylated had benefit to TMZ (see next slide?)

Perry NEJM, 376 2017
MGMT Story Not Entirely Clear: Methylation Status vs. Protein Expression

• n=452 patients on RTOG 0525
• Developed a Molecular-Based GBM RPA

• One Conclusion:
  MGMT protein expression more prognostic for survival than promoter methylation

Bell JAMA Onc Jan 12 2017
## My ‘Elderly’ GBM Treatment Schema

<table>
<thead>
<tr>
<th>KPS</th>
<th>My General Treatment Schema</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>TMZ + RT 60 Gy in 30 (Stupp)</td>
</tr>
<tr>
<td>Normal</td>
<td>TMZ + RT 40 Gy in 15 (Perry EORTC)</td>
</tr>
<tr>
<td>Mid</td>
<td>TMZ or RT single agent</td>
</tr>
<tr>
<td></td>
<td>TMZ alone: if MGMT methylated (Wick)</td>
</tr>
<tr>
<td></td>
<td>RT alone: if MGMT not methylated (Wick)</td>
</tr>
<tr>
<td></td>
<td>RT Options: 40 Gy in 15 (Roa)</td>
</tr>
<tr>
<td></td>
<td>34 Gy in 10 (Malmstrom)</td>
</tr>
<tr>
<td></td>
<td>25 Gy in 5 (Roa)</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab alone</td>
</tr>
<tr>
<td>Low</td>
<td>Supportive Care</td>
</tr>
</tbody>
</table>
Recurrent GBM
GBM Re-Irradiation

- n=147
- Median 35 Gy in 10 fractions to T1 post-contrast GTV
- Median OS – 11 m

Fig 1. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who experienced recurrence less than 6 months or ≥ 6 months from initial treatment.

Fig 2. Median survival time from hypofractionated stereotactic radiation therapy (H-SRT) of patients who received ≥ 35 Gy or < 35 Gy.

Fogh JCO 28, 2010
**RTOG 1205**

**Bevacizumab-Naïve Recurrent GBM Patients:**

<table>
<thead>
<tr>
<th>STRATIFY</th>
<th>RANDOMIZE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Arm 1: Bevacizumab alone q 2 weeks (control arm)</td>
</tr>
<tr>
<td>1.</td>
<td>Arm 2: Hypofractionated radiotherapy 35 Gy in 10 fractions with concurrent Bevacizumab q 2 weeks (experimental arm)</td>
</tr>
<tr>
<td>&lt;50</td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td></td>
</tr>
<tr>
<td>Karnofsky performance status</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>70-80</td>
<td></td>
</tr>
<tr>
<td>90-100</td>
<td></td>
</tr>
<tr>
<td>Recent resection</td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
| No/biopsy only | }
GBM Re-Irradiation

• n=25 single arm prospective

• BEV + 30 Gy in 5 fractions (QOD over 2 weeks)
  – GTV + 5mm PTV

• median OS 12.5 months

Gutin IJROBP 75, 2009
Recurrent GBM – Tumor Treating Fields (TTF)

- $n = 237$ rGBM
  - TTF
  - Best chemo

Stupp EuroJ Cancer 48, 2012
Newly Diagnosed GBM: Tumor Treating Fields (TTF)

- n=315 (interim report of 695 total)
  - Median OS
    - 60 Gy + TMZ → TMZ  15.6
    - 60 Gy + TMZ → TMZ + TTF  20.5
    - TTF >18 hours per day

*Patients randomized after Chemo-RT
(On Stupp, ~20% progressed by 3 months)

Stupp JAMA 314, 2015
Outline

• Glioma Molecular Overview
• Grade IV – Glioblastoma
  • Grade II and III Gliomas – Oligos and Astros
• Brain Metastases
• Benign and Misc. Tumors
New in 2016

- Grade III gliomas:
  - Molecular type trumps histology (most of the time)
  - Currently 3 main groups:
    - IDH mut 1p19q CODEL ATRX retained/p53 wt Oligo
    - IDH mut 1p19q intact ATRX loss/p53 mut Astro
    - IDH wt (1p19q intact) GBM
  - Therefore, mixed oligoastrocytoma is discouraged
New Molecular Era Make Old Data Confusing

• We now know that older trials that enrolled what was thought to be a homogeneous population (e.g., Grade II or Grade III tumors), actually had at least 3 different types

• To re-analyze past trials, incorporating what we now molecularly, is quite confusing, so bear with me on these next slides....
Anaplastic Oligodendrogliomas

In 2006 Sequential ChemoRT has no benefit over RT alone

<table>
<thead>
<tr>
<th>Citation</th>
<th>Arms</th>
<th>Median PFS (Years)</th>
<th>Median OS (Years)</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9402 Cairncross</td>
<td>59.4 Gy</td>
<td>1.7</td>
<td>4.7</td>
<td>PCV does not improve OS</td>
</tr>
<tr>
<td>JCO 24, 2006</td>
<td>iPCV x 4 $\rightarrow$ 59.4 Gy</td>
<td>2.6 (sig)</td>
<td>4.9 (NS)</td>
<td>PCV does improve PFS for 1p19q codeleted</td>
</tr>
<tr>
<td>EORTC 26951 van den Bent</td>
<td>59.4 Gy</td>
<td>1.1</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>JCO 24, 2006</td>
<td>59.4 Gy $\rightarrow$ PCV x 6</td>
<td>1.9 (sig)</td>
<td>3.4 (NS)</td>
<td></td>
</tr>
</tbody>
</table>
**Anaplastic Oligodendroglialomas**

**In 2012 Sequential ChemoRT better than RT alone**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Arms</th>
<th>Median OS (Years) 1p19q CODEL</th>
<th>Median OS (Years) 1p19q non-CODEL</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9402 Cairncross JCO 30, 2012</td>
<td>59.4 Gy</td>
<td>7.3</td>
<td>2.7</td>
<td>New Standard of Care.</td>
</tr>
<tr>
<td></td>
<td>iPCV x 4 → 59.4 Gy</td>
<td>14.7</td>
<td>2.6 (NS)</td>
<td>Sequential ChemoRT has no benefit in non-codeleted oligo (unless it is IDH-mut...see next slides)</td>
</tr>
<tr>
<td>EORTC 26951 van den Bent JCO 30, 2012</td>
<td>59.4 Gy</td>
<td>9.3</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>59.4 Gy → PCV x 6</td>
<td>Not Reached (Sig)</td>
<td>2.1 (NS)</td>
<td></td>
</tr>
</tbody>
</table>

- New standard of care: sequential RT → chemo if 1p19q codeleted, although from an unplanned analysis (i.e., 1p19q unknown in 1994)
- Role of TMZ vs. PCV is unknown
- Molecular Era thoughts: non-codeleted ‘Oligo’ is a grade III Astro – so at first read, this trial suggests no benefit with sequential PCV in *all* patients, but...
Non-codeleted Anaplastic ‘Oligo’ (really is an astro)

From 9402:
No benefit to adding chemo for all non-codeleted patients.

But appears to be of benefit in some non-codeleted patients (there is a separation in the tails)....
Sequential PCV $\rightarrow$ RT
Improves OS for IDH Mutant Astro or Oligo

<table>
<thead>
<tr>
<th>Arms (subset analysis of 9402)</th>
<th>Median OS (Years)</th>
<th>Median OS (Years)</th>
<th>Median OS (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Codeleted IDH1 Mutant</td>
<td>non-codeleted IDH1 Mutant</td>
<td>non-codeleted IDH1 wt</td>
</tr>
<tr>
<td>59.4 Gy</td>
<td>6.8</td>
<td>3.3</td>
<td>1.8</td>
</tr>
<tr>
<td>iPCV x 4 $\rightarrow$ 59.4 Gy</td>
<td>14.7 (sig)</td>
<td>5.5 (sig)</td>
<td>1.3 (NS)</td>
</tr>
</tbody>
</table>

Cairncross JCO 32, 2014

Fig 2. Kaplan-Meier estimates of overall survival for patients whose tumors were IDH mutated and 1p/19q codeleted (co-del; gold, mutated; blue), and nonmutated and noncodeleted (gray) after (A) procarbazine, vincristine, and cisplatin (PCV) plus radiotherapy (RT) and (B) RT alone. Median survivals after (A) PCV plus RT were 14.7 (95% CI, 6.4 to not reached), 3.2 (95% CI, 2.0 to 4.9), and 1.3 years (95% CI, 0.6 to 1.9; P < .001), respectively. Median survivals after (B) RT alone were 6.9 (95% CI, 5.4 to 9.0), 3.2 (95% CI, 2.0 to 4.9), and 1.3 years (95% CI, 0.6 to 1.9; P < .001), respectively.
### Sequential PCV → RT

**Improves OS for IDH Mutant Astro or Oligo**

<table>
<thead>
<tr>
<th>Arms (subset analysis of 9402)</th>
<th>Median OS (Years) Codeleted IDH1 Mutant</th>
<th>Median OS (Years) non-codeleted IDH1 Mutant</th>
<th>Median OS (Years) non-codeleted IDH1 wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.4 Gy</td>
<td>6.8</td>
<td>3.3</td>
<td>1.8</td>
</tr>
<tr>
<td>iPCV x 4 → 59.4 Gy</td>
<td>14.7 (sig)</td>
<td>5.5 (sig)</td>
<td>1.3 (NS)</td>
</tr>
<tr>
<td>Molecular Type</td>
<td>Oligo</td>
<td>Molecular Astro</td>
<td>Molecular GBM</td>
</tr>
</tbody>
</table>

Recall: Now know that cannot have an ‘Oligo’ that is not-codeleted

Benefit of PCV → RT over RT alone for grade III astro sounds similar to benefit of RT → TMZ over RT alone in CATNON (for grade III astros)
Standard of Care – Anaplastic Oligos

• Sequential RT → PCV or PCV → RT if:
  – 1p19q codeleted (molecular oligos)
    • MS 14.7 vs. 7.3 years
  – 1p19q non-codeleted, but IDH1 mutated (molecular astros)
    • MS 5.5 vs. 3.3 years
      – unknown if would benefit more from Stupp concurrent chemo (CATNON)?

• Non-codeleted, IDH1 wild type grade III (molecular GBM):
  – We know no benefit from sequential PCV
    • unknown if would benefit from Stupp concurrent chemo (CATNON)?
Grade II: Treatment Summary

• Old Answer:
  – Radiotherapy:
    • Overall – does not increase OS (Non-Believers)
    • Overall – does increase PFS (Non-Believers)
      – Main debate was on whether progression of tumor or the effect of RT was worse

• New Answer:
  – RTOG High risk (>40 years or STR) - RTOG 9802
    • Sequential 54 Gy → PCV better survival than 54 Gy alone
    • New Standard of Care if treating a LGG
    • Doesn’t define when to treat
  – Role of TMZ vs. PCV unknown: Maybe not equivalent (see NOA-04)
• Chemo-monotherapy should no longer be used (CODEL, NOA-04, EORTC)
## LGG: Extent of Resection

<table>
<thead>
<tr>
<th>Citation</th>
<th>Number of Patients</th>
<th>Extent of Resection (EOR)</th>
<th>Survival</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakola JAMA 2012</td>
<td>153</td>
<td>Biopsy</td>
<td>60% at 5 year</td>
<td>Population-based parallel cohorts at 2 hospitals (1 did biopsy, 1 did resection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resection</td>
<td>74% at 5 year</td>
<td></td>
</tr>
<tr>
<td>Smith JCO 26, 2008</td>
<td>216</td>
<td>&lt;90%</td>
<td>60% at 8 years</td>
<td>Greater EOR correlated with improved OS and lower rate of malignant transformation into HGG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;90%</td>
<td>91% at 8 years</td>
<td></td>
</tr>
<tr>
<td>Pallud Brain 137, 2014</td>
<td>1509</td>
<td>Biopsy</td>
<td>HR 1</td>
<td>Greater EOR correlated with improved OS and lower rate of malignant transformation into HGG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>STR</td>
<td>HR 0.62</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GTR</td>
<td>HR 0.32</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** Retrospective data support a goal of maximum safe resection.
LGG Radiotherapy – Timing and Dose

• What is the best timing (immediate vs. at recurrence):
  – EORTC 22845 - ‘Non-Believers’

• What is the best dose:
  – EORTC 22844 - ‘Believers’
  – NCCTG/RTOG/ECOG
‘Non-Believers’ – EORTC

- n=290
  - 60% Astro, 25% Oligo, 10% MOA

- 0 Gy
- 54 Gy

- CTV+2 cm to 45 Gy, CTV+1 cm to 54 Gy
- (Block edge margin ≠ 3D planning margin)
- Really is an upfront RT vs. RT at recurrence trial

Karim IJROBP 52, 2002
‘Non-Believers’ Update – PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>No early radiotherapy (n=157)</th>
<th>Early radiotherapy (n=154)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median years (95% CI)</td>
<td>7·4 (6·1–8·9)</td>
<td>7·2 (6·4–8·6)</td>
<td>0·97 (0·71–1·34)</td>
</tr>
<tr>
<td>Proportion alive at 5 years</td>
<td>65·7% (57·8–73·5)</td>
<td>68·4% (60·7–76·2)</td>
<td></td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median years (95% CI)</td>
<td>3·4 (2·9–4·4)</td>
<td>5·3 (4·6–6·3)</td>
<td>0·59 (0·45–0·77)</td>
</tr>
<tr>
<td>Proportion free from progression at 5 years</td>
<td>34·6% (26·7–42·5)</td>
<td>55·0% (46·7–63·3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Survival and progression-free survival

van den Bent Lancet 366, 2005
‘Non-Believers’ Update

• Therefore upfront RT improves PFS, but not OS

• Does improve seizures at 1 year:
  
<table>
<thead>
<tr>
<th>No XRT</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>41%</td>
<td>25%</td>
</tr>
</tbody>
</table>

• Does not increase the risk of transformation to GBM:

<table>
<thead>
<tr>
<th>No XRT</th>
<th>XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%</td>
<td>72% (NS)</td>
</tr>
</tbody>
</table>
‘Believers’ – EORTC

• n=379
• Randomized after surgery:
  – 60% Astro, 22% Oligo, 10% MOA

• 45 Gy
• 59.4 Gy

• CTV+2 to 45 Gy, CTV+1 to 54 Gy, CTV+0 to 59.4 Gy

Karim IJROBP 36, 1996
Fig. 1. (a) Survival and (b) progression-free survival (PFS) of patients treated with a low dose (45 Gy) and high dose (59.4 Gy).

- Conclusion: No dose response at 45 Gy vs. 59.4 Gy

Karim IJROBP 36, 1996
NCCTG/RTOG/ECOG

• n=203
  - 95% LGG, 5% Grade I

• 50.4 Gy
• 64.8 Gy

• CTV+2 to 50.4, CTV+1 to 64.8

Shaw JCO 20, 2002
Fig 1. Kaplan-Meier (K-M) estimates of overall survival by treatment arm for patients receiving low-dose (arm A) or high-dose radiation therapy (arm B). Two-sided log rank test *P* = .48. N(t), number of patients; Si(t), K-M survival; Cl, 95% confidence interval.

Fig 5. Kaplan-Meier estimates of time to occurrence of grade 3 (severe), grade 4 (life-threatening), or grade 5 (fatal) radiation neurotoxicity by treatment arm (low-dose or high-dose radiation therapy). N(t), number of patients; F(t), K-M estimate of severe or greater neurotoxicity; Cl, 95% confidence interval.

Shaw JCO 20, 2002
LGG: Dose and Volumes

• Current trials (EORTC, RTOG) use 50.4 – 54 Gy
• RTOG 1072:
  – 50.4 Gy in 1.8 Gy
  – GTV = resection cavity + any T2/FLAIR
  – CTV = GTV + 1 cm (not extending outside brain)
  – PTV = CTV + 0.5 cm
LGG: Risk Stratification

- EORTC High Risk is 3-5 High Risk Features:
  1. Age $\geq 40$ yo
  2. Diameter $\geq 6$ cm
  3. Tumor crosses midline
  4. Astrocytoma (not oligo)
  5. Neurologic Symptoms prior to surgery

- Median OS:
  - 0-2 features $7.7$ years
  - 3-5 features $3.2$ years

Pignatti JCO 20, 2002
Chemo-RT Combined Modality Treatment:
RTOG 0424 – High Risk LGG with RT/TMZ

- n=129 LGG with 3-5 EORTC/Pignatti risk factors
- **Single arm**: 54 Gy + TMZ $\rightarrow$ TMZ (Stupp chemo)
- Goal: TMZ will improve 3-year overall survival (OS) rate from 54% (historical control) to 65% at a 10% significance level (1-sided) and 96% power.

- Results at 4.1 year median F/U:
  - MS not reached
  - 3y OS 73% (greater than the 54% historical control)

- **Hypothesis Generating Trial**

Fisher IJROBP 91, 2015
RTOG 9802: RT vs. RT → PCV for High Risk LGG

High Risk: Age > 40 or Sub-total resection

<table>
<thead>
<tr>
<th>Citation</th>
<th>Arms</th>
<th>Median PFS (Years)</th>
<th>Median OS (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shaw JCO 30, 2012</td>
<td>54 Gy</td>
<td>4.4</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>54 Gy → PCV x 6</td>
<td>(Sig) p=0.005</td>
<td>(NS) p=0.13</td>
</tr>
<tr>
<td>Buckner NEJM 374, 2016</td>
<td>54 Gy</td>
<td>4.0</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>54 Gy → PCV x 6</td>
<td>10.4 (Sig)</td>
<td>13.3 (Sig)</td>
</tr>
</tbody>
</table>
RTOG 9802 High Risk LGG: RT vs RT → PCV

• n=251

• RTOG High risk LGG: >40 years or STR
  – 26% Astro, 43% oligo, 31% MixedOA*
  – 62% IDH mut, 37% IDH wt*
    *Now know molecularly can’t have MOA, and IDH wt is ~GBM
    *Now know from 9402 that IDH wt did not benefit from PCV

• RT (54 Gy to 2cm to block edge)
• RT → PCV x 6

Buckner NEJM 374, 2016
RTOG 9802 High Risk LGG: RT vs RT → PCV

Median OS (y) 10y OS

- RT  7.8  40
- RT → PCV x 6  13.3  60

Buckner NEJM 374, 2016
RTOG 9802 High Risk LGG: RT vs RT → PCV

Median OS (y)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Oligos</th>
<th>Astro</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>7.8</td>
<td>HR 0.43</td>
</tr>
<tr>
<td>RT → PCV x 6</td>
<td>13.3</td>
<td>p=0.009</td>
</tr>
</tbody>
</table>

B Overall Survival, Grade 2 Oligodendroglioma

D Overall Survival, Grade 2 Astrocytoma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients Who Died</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT+PCV</td>
<td>14</td>
<td>50</td>
</tr>
<tr>
<td>RT Alone</td>
<td>32</td>
<td>57</td>
</tr>
</tbody>
</table>

Hazard ratio, 0.43 (95% CI, 0.23–0.82) P=0.009
RTOG 9802: Integrating Histologic with Molecular Type

Table S2. Frequency of IDH1 132H Mutations by Histologic Type.

<table>
<thead>
<tr>
<th>IDH</th>
<th>Astrocytoma n</th>
<th>%</th>
<th>Oligoastrocytoma n</th>
<th>%</th>
<th>Oligodendroglioma n</th>
<th>%</th>
<th>Total n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>13</td>
<td>52.0</td>
<td>18</td>
<td>46.2</td>
<td>11</td>
<td>22.4</td>
<td>42</td>
<td>37.2</td>
</tr>
<tr>
<td>Positive</td>
<td>12</td>
<td>48.0</td>
<td>21</td>
<td>53.8</td>
<td>38</td>
<td>77.6</td>
<td>71</td>
<td>62.8</td>
</tr>
</tbody>
</table>

But if not IDH mutant, then not really a low grade glioma....
So many of the ‘low grade astrocytomas’ had outcomes of GBM...

Buckner NEJM 374, 2016
RTOG 9802 High Risk LGG: RT vs RT → PCV

Median OS (y) IDH1 Mutants

- RT  7.8  HR 0.42
- RT → PCV x 6  13.3  p=0.02

Too few events to analyze if chemo helps IDH1 wildtype

1p19q only available in 25%, so can’t analyze outcomes

Buckner NEJM 374, 2016
RTOG 9802 High Risk LGG: RT vs RT → PCV

• Therefore Sequential RT → PCV:
  – Is standard of care for High Risk LGG Overall
  – Main benefit is in histologic oligos (but don’t have 1p19q on them)
  – Main benefit is in IDH1 mut (but don’t know if these were oligos or astros)
  – Don’t know if PCV helps IDH wt
    • Recall 9402 where PCV improved OS for:  G3 Oligo (IDH mut, Codeleted)
       G3 Astro (IDH mut, not codeleted)
       NOT for IDH wt
  General theme is PCV improves OS if you live for over 5 years

Buckner NEJM 374, 2016
RTOG 9802: Standard of Care for High Risk LGG

Summary:

• Similar to 9402 as initially negative, but now positive for OS
• Similar to 9402: Sequential RT → chemo better than RT alone for OS
  • RTOG 9802: OS 7.8 vs. 13.3 years for histologic LGG
  • RTOG 9402: OS 7.3 vs. 14.7 years for Oligo subgroup

• RTOG 9802 tells you how to treat, but not when to treat
  – e.g., I’ll observe a 41 yo with a GTR of a right frontal, non-eloquent oligo
Overall Grade II/III Glioma Theme

• Previously, focused on Chemo (or RT) monotherapy to reduce toxicity, since nothing proven to improve OS
• Today, now seeing improve OS with combined modality:
  – Grade II: RTOG 9802
  – Grade III: RTOG 9402, EORTC 26951
  – Grade IV: Stupp
• Still don’t know how to fully integrate molecular features (or how to re-interpret past data in the molecular era)
• Unclear if TMZ is comparable to PCV
EORTC 22033-26033: Grade II RT or TMZ monotherapy

• n=477  Grade II – Astro, Oligoastro, Oligo
• at least 1 High Risk feature
  (>40y, progression, Refractory Seizures, Neuro Symptoms)
• RT 50.4 Gy
• TMZ alone (dose dense - 75 mg/m², 21 of 28 days)
• Primary: PFS

Baumert Lancet Onc 17, 2016
EORTC 22033-26033: Grade II RT or TMZ monotherapy

**PFS (y)**

- RT 50.4 Gy alone: 3.8
- ddTMZ alone: 3.3 \(p=0.22\)

**Conclusions:**

- For PFS, no difference with TMZ vs. RT
  - Too early for OS (only 25% have died)
  - Subgroup Analyses:
    - Astro (IDHmt/Non-codel) TMZ worse than RT
    - Molecular type more prognostic than histology

[Baumert Lancet Onc 17, 2016](#)
General Theme in Gliomas: Combined Chemo-RT appearing better than Monotherapy

Data suggest that sequential chemoRT better than RT or Chemo monotherapy:

• For grade II: ChemoRT on RTOG 9802 better than monotherapy on EORTC 22033-26033
• For grade III: ChemoRT on RTOG 9402/EORTC 26951 better than monotherapy on NOA-04
NOA-04 Grade 3 – Sequential Single Agent Trial

n=318     Grade 3  1999-2005
– 53% AA
– 33% AOA
– 14% AO

• 59.6-60 Gy to GTV+2cm
• Primary Endpoint:
  – Time to Treatment Failure (TTF)
    • Progressed after both RT and Chemo

Wick JCO 27, 2009
NOA-04 Grade 3 – Sequential Single Agent Trial

- No difference in TTF with chemo 1\textsuperscript{st} or RT 1\textsuperscript{st}
- AA worse than AO, but AO same as mixed AOA
  - 2016 – now know that mixed AOA ~doesn’t exist
- No difference in PCV vs. TMZ
  - but not powered for comparison between PCV and TMZ

Wick JCO 27, 2009
NOA-04 Grade 3 Sequential Single Agent – 2016 Update

• We now know of the 3 molecular types of grade 3 glioma:
  
  – IDH mutant 1p19q CODEL ATRX retained/p53 wt  
  – IDH mutant 1p19q intact ATRX loss/p53 mut  
  – IDH wildtype

Wick NeuroOnc 18, 2016
NOA-04 Grade 3 Sequential Single Agent – 2016 Update

Background: For those with best prognosis (1p19q co-deleted oligos), many advocate for single agent chemo to avoid long term risks of RT

NOA-04 offers opportunity to look at monochemotherapy vs. RT based on molecular type

Wick NeuroOnc 18, 2016
NOA-04 Grade 3 Sequential Single Agent – 2016 Update

Median Follow-up:

• In 2009 5.4 y
• In 2016 9.5 y

– Endpoints reached: Progression 78%
  TTF 67%
  OS ~50%
NOA-04 Grade 3 Sequential Single Agent – 2016 Update

- No differences between chemo or RT arms in PFS, TTF, OS

**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 NeuroOnc 18, 2016
NOA-04 Grade 3 Sequential Single Agent – 2016 Update

For both Astros or Oligos:
OS same for Chemo or RT first

For Oligos: OS maybe worse for TMZ vs PCV (p=0.07)

Supplement in Wick NeuroOnc 18, 2016
NOA-04 Grade 3 Sequential Single Agent – 2016 Update

• 3 molecular types are more prognostic than histologic types:

  - AO or AOA
  - AA
  - IDHMut, Codel
  - IDHMut Not Codel
  - IDH wt

Supplement in Wick NeuroOnc 18, 2016
Other points:

- MGMT + had improved PFS in chemotherapy-treated patients only in IDH-wildtype tumors (astros/GBM).
  - In IDH mutant tumors (either astro or oligo), MGMT was + in almost all (85% in astro and 91% in oligo) and neither prognostic nor predictive
- Data suggest TMZ monotherapy worse than RT or PCV monotherapy
Conclusions:

- Monochemotherapy not better than primary RT
- For 1p19q co-deleted, NOA-04 supports:
  - Sequential chemoradiotherapy per RTOG 9402, 9802 and EORTC 26951
    - Because Chemo same as RT in NOA-04, but Sequential ChemoRT better than RT alone on RTOG/EORTC (if A=B, but C is better than B, then C is better than A)
  - PCV possibly better than TMZ in Oligos
    - Await the current CODEL trial of PCV vs. TMZ
- ‘Closing the book on monochemotherapy’
  - Controversial, as we have no prospective controlled data
  - But, also see the closed TMZ alone arm on CODEL
  - See concerns about hypermutation with TMZ (next slide)
Concerns with TMZ monotherapy: Hypermutated State from TMZ in LGG

- Exome sequencing in 23 LGG tumors and at the time of transformation to GBM
  - 10 patients treated with TMZ monotherapy
    - 6 of those were hypermutated when GBM
      - 97% of those were mutations characteristic of TMZ
      - Led to driver mutations in a pathway to GBM different than in non-TMZ patients

Johnson Science 343, 2014
Original CODEL Trial

1p19q Grade 3 CODEL Tumors

Original

1. RT (59.6 Gy)
2. RT + TMZ → TMZ (Stupp)
3. TMZ x 12
Original CODEL Trial

1p19q Grade 3 CODEL Tumors

Original

1. RT (59.6 Gy)
2. RT + TMZ $\rightarrow$ TMZ (Stupp)
3. TMZ x 12

But: EORTC/RTOG 9402, RT alone worse than RT $\rightarrow$ PCV

And with results in 36 patients, with 3.5y F/U*:

Progression 58 vs 13% on TMZ vs. RT arms, with worse OS

Conclusion: Change the RT alone arm, CLOSE the TMZ alone arm

*Neurology Supplement April 5, 2016
Current CODEL Trial

1p19q Grade 3 CODEL Tumors or 9802 High Risk grade 2 oligos

Current

1. RT (59.6 Gy) → PCV*
2. RT + TMZ → TMZ (Stupp)
3. TMZ x 12

Primary: PFS

*Therefore testing:
Stupp vs. standard of care of sequential RT → PCV
(per 9802 (grade 2) and 9402 (grade 3))
CATNON: Grade 3 Non-Codeleted

• n=748, Grade 3 NOT codeleted (i.e., Anaplastic Astros)
  – RT 59.4 Gy
  – RT 59.4 Gy + TMZ concurrent
  – RT 59.4 Gy \rightarrow TMZ x 12 adjuvant
  – RT 59.4 Gy + TMZ concurrent \rightarrow TMZ x 12 adjuvant (Stupp)

Interim Analysis (only of adjuvant arms)*:

• **Adjuvant** TMZ improved OS (HR 0.65): 5yr OS 56 vs. 44%
• Need more follow-up to determine role of concurrent TMZ

Van Den Bent ASCO 2016 Plenary
My Current Algorithm....
<table>
<thead>
<tr>
<th>Histology and Grade</th>
<th>Molecular Type</th>
<th>My Treatment (Mostly data-based)</th>
<th>Median OS (years)</th>
<th>Citation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2 Astro</td>
<td>IDH Mutant 1p19q not codeleted ATRX loss, p53 mut</td>
<td>54 Gy to 1.5 cm → Chemo</td>
<td>6+</td>
<td>RTOG 9802</td>
<td>9802: PCV of benefit if IDHmt</td>
</tr>
<tr>
<td>G3 Astro</td>
<td>IDH Mutant 1p19q not codeleted ATRX loss, p53 mut</td>
<td>59.4 Gy to 2 cm → Chemo (Consider Stupp Chemo)</td>
<td>5+</td>
<td>RTOG 9402</td>
<td>9402: PCV of benefit if IDHmt</td>
</tr>
<tr>
<td>G2 Oligo</td>
<td>IDH Mutant 1p19q codeleted ATRX retained, p53 wt</td>
<td>54 Gy to 1.5 cm → Chemo</td>
<td>14+</td>
<td>RTOG 9802</td>
<td>Grade is likely not prognostic in Oligos.</td>
</tr>
<tr>
<td>G3 Oligo</td>
<td>IDH Mutant 1p19q codeleted ATRX retained, p53 wt</td>
<td>59.4* Gy to 2 cm → Chemo Chemo → 59.4* Gy to 2 cm *probably can do 54Gy?</td>
<td>14+</td>
<td>RTOG 9402 EORTC26951</td>
<td></td>
</tr>
<tr>
<td>G2/3</td>
<td>IDH wt*</td>
<td>Consider 59.4 Gy to 1.5 cm + Stupp Chemo</td>
<td>~2+</td>
<td>RTOG 9402 RTOG 9802 RTOG 0424</td>
<td>No benefit to adj PCV. Extrapolate from Stupp, as OS is ~GBM</td>
</tr>
<tr>
<td>G4</td>
<td>GBM IDH wt GBM IDH mut</td>
<td>60 Gy to 2 cm + Stupp Chemo</td>
<td>~2</td>
<td>Stupp NEJM Stupp JAMA</td>
<td>Offer TTF</td>
</tr>
</tbody>
</table>
Other Algorithms – May Quickly Be Outdated

Reifenberger Weller
Nature Rev Clinic Onc Dec 2016

Anaplastic Gliomas\textsuperscript{a}/Glioblastoma

ANAPLASTIC GLIOMAS

PATHOLOGY\textsuperscript{d}

ADJUVANT TREATMENT

1p19q codeleted:
Anaplastic oligodendroglioma
Anaplastic oligoastrocytoma

Fractionated external beam RT\textsuperscript{k} and neoadjuvant or adjuvant PCV chemotherapy (category 1)\textsuperscript{m}

1p19q uni- or non-deleted:
Anaplastic oligodendroglioma
Anaplastic oligoastrocytoma
Anaplastic astrocytoma

Fractionated external beam RT\textsuperscript{k} (category 1) or Fractionated external beam RT\textsuperscript{k} and temozolomide chemotherapy\textsuperscript{m} or PCV or temozolomide chemotherapy\textsuperscript{m}

Anaplastic gliomas
Poor performance status (KPS <60)

Fractionated external beam RT\textsuperscript{k} (hypofractionated [preferred] or standard) or PCV or temozolomide chemotherapy (category 2B)\textsuperscript{m}

Palliative/Best supportive care
Unknowns

- When to treat (how does observation impact OS)
- How best to treat IDH wt grade II and III (a molecular GBM)
- How does TMZ compare with PCV
- Should we reduce the grade III oligo dose down to 54 Gy?
  - 13+ year OS for Grade II is same as Grade III
    - Grade II 54 Gy (RTOG 9802) and Grade III 59.4 Gy (RTOG 9402)
  - See NRG Trial Concept: PI- Grosshans Proton vs. Photons
    - All IDH mt (G2/3), All get 54Gy and adjuvant TMZ
- No long term cognitive data for combined Chemo-RT
Outline

• Glioma Molecular Overview
• Grade IV – Glioblastoma
• Grade II and III Gliomas – Oligos and Astros
  • Brain Metastases
• Benign and Misc. Tumors
**Brain Metastases – Key Points**

- **Post-op RT** is needed following a gross total resection
  
  Local Failure 55-65% with GTR alone

- **WBRT**
  
  - no data to show that it improves OS (but no trial powered for OS)
  
  Improves local control compared to SRS/Surgery alone
  
  Improves rate of new brain metastases
  
  If SRS alone → ~50% new met in 1 year
  
  Improves neurologic death rate (in 2 of 3 trials)
  
  14-28% with WBRT; 44% without WBRT

- **Local intensification** (Surgery or SRS) does improve OS if added to WBRT
  
  But only in good KPS patients or single metastasis

- **Intracranial progression** – leads to cognitive dysfunction

- **WBRT** – leads to cognitive dysfunction (more than progression – Brown)
Decadron Dose – Randomized Trial

- n=96, brain met, KPS<80
- **Dose (Total QD)** | **Improved KPS (points)**
  - 16mg | 7.3 (1w)
  - 8mg  | 8.0 (1w)
  - 16mg | 9.1 (1w) 5.6 (4w)
  - 4mg  | 6.7 (1w) 7.1 (4w)

- 16mg more toxic ($p<.03$)
- Therefore, if high dose is needed, then do 8mg BID x 1 week, but can usually quickly drop to 2mg BID in most patients

Vecht Neurology 44, 1994
Brain Metastases - RPA

- Brain Met RPA
  - Class I: <65yo
    - KPS>70
    - Controlled Primary
    - No extracranial mets
    - Incidence: 20% MS 7.1 m
  - Class II: Not I or III
    - Incidence: 65% MS 4.2 m
  - Class III: KPS<70
    - Incidence: 15% MS 2.3 m
  - n=1200

Gaspar IJROBP 37, 1997
GPA: Graded Prognostic Assessment

- developed from n=1960 RTOG patients

More objective that RPA, as don’t need to know systemic disease status

Table 4. Graded Prognostic Assessment

<table>
<thead>
<tr>
<th>GPA</th>
<th>n</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 - 4</td>
<td>102</td>
<td>11.0</td>
</tr>
<tr>
<td>3</td>
<td>168</td>
<td>6.9</td>
</tr>
<tr>
<td>1.5 - 2.5</td>
<td>666</td>
<td>3.8</td>
</tr>
<tr>
<td>0 - 1</td>
<td>143</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Score

<table>
<thead>
<tr>
<th>Score</th>
<th>GPA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;60</td>
<td>50–59</td>
</tr>
<tr>
<td>0.5</td>
<td>&lt;70</td>
<td>70–80</td>
</tr>
<tr>
<td>1.0</td>
<td>&gt;3</td>
<td>90–100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Score</th>
<th>GPA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;3</td>
<td>2–3</td>
</tr>
<tr>
<td>0.5</td>
<td>Present</td>
<td>None</td>
</tr>
</tbody>
</table>

Sperduto IJROBP 70, 2008
## Disease Specific GPA

### Non-small-cell and small-cell lung cancer

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>≥ 60</td>
<td>0.5, 1.0</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80, 90-100</td>
</tr>
<tr>
<td>ECM</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>No. of BM</td>
<td>&gt; 3</td>
<td>2, 3</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Median survival (months) by GPA:** 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

### Melanoma

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80, 90-100</td>
</tr>
<tr>
<td>No. of BM</td>
<td>&gt; 3</td>
<td>2, 3</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Median survival (months) by GPA:** 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

### Breast cancer

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>≤ 50</td>
<td>70-80, 90-100</td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal n/a</td>
<td>LumA HER2 LumB</td>
</tr>
<tr>
<td>Age, years</td>
<td>≥ 60</td>
<td>&lt; 60 n/a n/a n/a</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Median survival (months) by GPA:** 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

### Renal cell carcinoma

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70-80, 90-100</td>
</tr>
<tr>
<td>No. of BM</td>
<td>&gt; 3</td>
<td>2, 3</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Median survival (months) by GPA:** 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

### GI cancers

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>&lt; 70</td>
<td>70, 80, 90, 100</td>
</tr>
</tbody>
</table>

**Median survival (months) by GPA:** 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5
# 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>Survival Time (months)</th>
<th>No. of Patients</th>
<th>Survival Time (months)</th>
<th>Patients</th>
<th>Survival Time (months)</th>
<th>Patients</th>
<th>Survival Time (months)</th>
<th>Patients</th>
<th>Survival Time (months)</th>
<th>Patients</th>
<th>Survival Time (months)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diagnosis</td>
<td>Median</td>
<td>95% CI</td>
<td>No. of Patients</td>
<td>Median</td>
<td>95% CI</td>
<td>No.</td>
<td>Median</td>
<td>95% CI</td>
<td>No.</td>
<td>Median</td>
<td>95% CI</td>
<td>No.</td>
</tr>
<tr>
<td>NSCLC</td>
<td></td>
<td>7.00</td>
<td>6.53 to 7.50</td>
<td>1,833</td>
<td>2.63</td>
<td>2.84</td>
<td>254</td>
<td>5.49</td>
<td>4.83 to 6.40</td>
<td>705</td>
<td>38.94</td>
<td>8.38 to 10.80</td>
<td>713</td>
</tr>
<tr>
<td>SCLC</td>
<td></td>
<td>4.90</td>
<td>4.30 to 6.20</td>
<td>281</td>
<td>2.79</td>
<td>3.12</td>
<td>252</td>
<td>4.90</td>
<td>4.04 to 6.51</td>
<td>119</td>
<td>42.76</td>
<td>6.27 to 9.13</td>
<td>84</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td>5.74</td>
<td>5.90 to 7.50</td>
<td>481</td>
<td>3.38</td>
<td>4.27</td>
<td>84</td>
<td>4.70</td>
<td>4.07 to 5.59</td>
<td>150</td>
<td>31.87</td>
<td>6.74 to 10.77</td>
<td>135</td>
</tr>
<tr>
<td>RCC</td>
<td></td>
<td>9.63</td>
<td>7.86 to 10.91</td>
<td>286</td>
<td>3.27</td>
<td>5.10</td>
<td>43</td>
<td>7.29</td>
<td>3.73 to 10.91</td>
<td>76</td>
<td>27.11</td>
<td>8.80 to 14.80</td>
<td>104</td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td>13.80</td>
<td>11.53 to 15.87</td>
<td>400</td>
<td>3.35</td>
<td>3.78</td>
<td>23</td>
<td>7.70</td>
<td>5.62 to 8.74</td>
<td>104</td>
<td>26.15</td>
<td>12.94 to 15.87</td>
<td>140</td>
</tr>
<tr>
<td>GI Cancer</td>
<td></td>
<td>5.36</td>
<td>4.30 to 6.30</td>
<td>209</td>
<td>3.13</td>
<td>4.57</td>
<td>75</td>
<td>4.40</td>
<td>3.76 to 6.53</td>
<td>65</td>
<td>31.68</td>
<td>4.86 to 11.63</td>
<td>50</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>6.37</td>
<td>5.22 to 7.49</td>
<td>450</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>7.16</td>
<td>6.83 to 7.52</td>
<td>3,940</td>
<td>3.10</td>
<td>3.45</td>
<td>545</td>
<td>5.40</td>
<td>4.90 to 5.89</td>
<td>1,219</td>
<td>35.96</td>
<td>8.74 to 10.58</td>
<td>1,226</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.*
Controversy: Size vs. Number?

Which is worse for survival?

10 mets x 1 cm

2 mets x 2cm
Controversy: Size vs. Number?

Which is worse for survival?

10 mets x 1 cm = 5 cc

2 mets x 2 cm = 8.4 cc
Volume is More Important than Number

<table>
<thead>
<tr>
<th>Citation</th>
<th>Volume of Metastases</th>
<th>Number of Metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhatnagar IJROBP 2006</td>
<td>p = 0.002</td>
<td>p = 0.3 (NS)</td>
</tr>
<tr>
<td>Likhacheva IJROBP 2012</td>
<td>p &lt;0.001</td>
<td>p = 0.2 (NS)</td>
</tr>
<tr>
<td>Baschnagel JNS 2013</td>
<td>p = 0.003</td>
<td>p = 0.1 (NS)</td>
</tr>
<tr>
<td>Choi IJROBP 2012</td>
<td>p = 0.01</td>
<td>p = NS</td>
</tr>
</tbody>
</table>
SRS for 1 – 10 Metastases: Prospective

- n=1194
- 1-10 metastases treated with SRS alone
- Survival non-inferior for 5-10 vs. 2-4 metastases
- Leptomeningeal Disease 13%
- WBRT 9%
Brain Metastases – Treatment Options

• Surgery
• WBRT
• WBRT + Surgery
• WBRT + SRS
• SRS
• Surgery \to SRS
Brain Metastases – Treatment Options

- Surgery
- WBRT
- WBRT + Surgery
- WBRT + SRS
- SRS
- Surgery → SRS

Question: Is surgery alone (without WBRT) adequate treatment?
Brain Metastases: Surgery +/- WBRT

• n=95
  – Single met, KPS>70, GTR by MRI

• Surgery

• Surgery + WBRT (50.4 Gy in 1.8)

Patchell JAMA 17:280, 1998
## Brain Metastases: Surgery +/- WBRT

- **n=95**

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>All Brain</th>
<th>Local Control</th>
<th>Distant Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>11 m</td>
<td>70</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Surgery + WBRT</td>
<td>12 m</td>
<td>18</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

- Primary endpoint: LC (not survival)

**Crude Incidence of Recurrence**

Patchell JAMA 17:280, 1998
Brain Metastases: Surgery +/- WBRT

- n=95

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
<th>All Brain</th>
<th>Local Control</th>
<th>Distant Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>11 m</td>
<td>70</td>
<td>46</td>
<td>37</td>
</tr>
<tr>
<td>Surgery + WBRT</td>
<td>12 m</td>
<td>18</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

- But, the above are crude incidences.
- The actual curves show:

  - 1yr rate
    - Surg: LF 66% DF 50%
    - Surg+WBRT: LF 20% DF 18%

Patchell JAMA 17:280, 1998
Brain Metastases: Surgery +/- WBRT

1 yr Local Failure:

Surgery  ~66%
Surgery + WBRT  ~20%

Patchell JAMA 17:280, 1998
Brain Metastases: Surgery +/- WBRT

1 yr Distant Failure:

Surgery ~50%

Surgery + WBRT ~18%

Patchell JAMA 17:280, 1998
Brain Metastases: Surgery +/- WBRT

- n=95

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neurologic</td>
</tr>
<tr>
<td>Surgery</td>
<td>44%</td>
</tr>
<tr>
<td>Surgery+WBRT</td>
<td>14%</td>
</tr>
</tbody>
</table>

- No difference in Functionally Independent Survival or OS

Patchell JAMA 17:280, 1998
EORTC 22952-26001

- n=359
- 1-3 Metastases
- Stable systemic disease
- WHO PS 0-2

Kocher JCO 29, 2011
EORTC 22952-26001

- SRS
- SRS + WBRT (30Gy)
- Surgery
- Surgery + WBRT (30Gy)

SRS: GTV + 1-2mm to 20Gy
3.5cm max or 2.5cm if multiple

Surgery: GTR required (surgeon defined or MRI)

Primary Outcome:
Duration of Functional Independence (Time to WHO PS>2)

~Aoyama
~Patchell

Kocher JCO 29, 2011
FIS Median:
- No WBRT: 9.5m
- WBRT: 10.0m (NS)

OS Median:
- No WBRT: 10.9m
- WBRT: 10.7m (NS)

Neurologic death:
- No WBRT: 44%
- WBRT: 28% (Sig)

Kocher JCO 29, 2011
24 Month failure:

- **Surgery**
  - Local: 59
  - Distant: 42
- **Surgery+WBRT**
  - Local: 27
  - Distant: 23
- **SRS**
  - Local: 31
  - Distant: 48
- **SRS + WBRT**
  - Local: 19
  - Distant: 33

---

*Kocher JCO 29, 2011*
• WBRT does not improve:
  – functionally independent survival
  – overall survival

• WBRT does improve:
  – Local Control
  – Distant intracranial control
  – Neurologic death rate
# Surgery Alone vs. With WBRT/SRS

<table>
<thead>
<tr>
<th>Citation</th>
<th>1 yr Local Failure *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery alone</td>
</tr>
<tr>
<td>Patchell JAMA 1998</td>
<td>66</td>
</tr>
<tr>
<td>Kocher JCO 2010</td>
<td>55</td>
</tr>
<tr>
<td>Mahajan MDACC ASTRO 2016</td>
<td>55</td>
</tr>
</tbody>
</table>

* Rates Approximated from Survival Curves
Brain Metastases – Treatment Options

- Surgery
- WBRT
- WBRT + Surgery
- WBRT + SRS
- SRS
- Surgery → SRS

Question: How does intensification of local treatment with surgery help?
# Brain Metastases: WBRT +/- Surgery

<table>
<thead>
<tr>
<th>Citation</th>
<th>Outcome</th>
<th>WBRT</th>
<th>WBRT + Surgery</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchell NEJM 322, 1990</td>
<td>Local Failure %</td>
<td>52</td>
<td>20</td>
<td>Surgery improves OS for single met</td>
</tr>
<tr>
<td></td>
<td>Median OS (months)</td>
<td>4</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Vecht Ann Neuro 33, 1993</td>
<td>Median OS (months)</td>
<td>6</td>
<td>10</td>
<td>Surgery improves OS for single met only if controlled systemically</td>
</tr>
<tr>
<td></td>
<td>Median OS (months)</td>
<td>7</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controlled systemically</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median OS (months)</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uncontrolled systemically</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mintz Cancer 78, 1996</td>
<td>Median OS (months)</td>
<td>6</td>
<td>6</td>
<td>Worse KPS and not controlled systemically</td>
</tr>
</tbody>
</table>
Brain Metastases – Treatment Options

• Surgery
• WBRT
• WBRT + Surgery
• WBRT + SRS
• SRS
• Surgery \(\rightarrow\) SRS

Question: How does intensification of local treatment with SRS help?
SRS Dosing: RTOG 9005

• n=156
• Dose escalation trial to find Maximum Tolerated Dose (MTD) of SRS

• Recurrent metastases or primary brain tumors
  – i.e., ALL had prior RT (~60 Gy or 30 Gy) a median 17 months prior to SRS*

• *A common question is if we need to alter our WBRT dose/plan to account for past SRS → No, as our SRS dose is based on those that had prior RT

Shaw IJROBP 47: 291, 2000
# SRS Dosing: RTOG 9005 Results

## Incidence of Grade 3, 4, and 5 CNS Toxicity

<table>
<thead>
<tr>
<th>Tumor size*</th>
<th>Arm</th>
<th>Dose</th>
<th>No. of patients</th>
<th>% of Patients With Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>≤ 20 mm</td>
<td>1</td>
<td>18 Gy</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>21 Gy</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>24 Gy</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>21–30 mm</td>
<td>2</td>
<td>15 Gy</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>18 Gy</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>21 Gy</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>24 Gy</td>
<td>12</td>
<td>33</td>
</tr>
<tr>
<td>31–40 mm</td>
<td>3</td>
<td>12 Gy</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>15 Gy</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>18 Gy</td>
<td>18</td>
<td>17</td>
</tr>
</tbody>
</table>

* Maximum tumor diameter.

**FINAL Recommendations:**

- <2 cm: 24 Gy
- 2.1-3.0 cm: 18 Gy
- 3.1-4.0 cm: 15 Gy

Shaw IJROBP 47: 291, 2000
RTOG 9508 Brain Metastases: WBRT +/- SRS

- n=333 1-3 metastases  KPS >70

- WBRT 37.5 Gy in 15 fractions

- WBRT + SRS
  - 1 week after WBRT. SRS dose: 24Gy, 18Gy, 15Gy per RTOG 9005

- Primary endpoint: Survival
  - Secondary: Tumor LC, Brain Control, KPS

Andrews Lancet 363, 2004
MST = mean survival time.

Figure 2: Intention-to-treat outcomes by tumour size, extent of intracranial disease, radiation dose, and treatment technique.

Andrews Lancet 363, 2004
Conclusion:

SRS improves overall survival for those with a single metastasis.
Brain Metastases – Treatment Options

• Surgery
• WBRT
• WBRT + Surgery
  • WBRT + SRS
  • SRS
• Surgery → SRS

Question: What does WBRT add to SRS?
<table>
<thead>
<tr>
<th>Citation</th>
<th>Median OS (Months)</th>
<th>SRS</th>
<th>SRS + WBRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama JAMA 295, 2006</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Local Control (1 year)</td>
<td>73</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>Distant Control (1 year)</td>
<td>64</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Neurologic Death</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Chang Lancet Onc 2009</td>
<td>Cognitive Decline (HVLT at 4 months)</td>
<td>24</td>
<td>52</td>
</tr>
<tr>
<td></td>
<td>Median OS (months)</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Distant Control (1 year)</td>
<td>45</td>
<td>73</td>
</tr>
<tr>
<td>Brown JAMA 316, 2016</td>
<td>Cognitive Decline at 3 m</td>
<td>64</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>Intracranial Control 1 y</td>
<td>51</td>
<td>85</td>
</tr>
<tr>
<td>Kocher JCO 29, 2011</td>
<td>Previously reviewed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NCCTG N0574: SRS vs. SRS + WBRT

- n=213
- 1-3 metastases, each <3cm
- Endpoint: Cognitive Deterioration at 3 months
  - (>1 SD in any of 6 cognitive tests)

<table>
<thead>
<tr>
<th></th>
<th>@ 3m</th>
<th>@12m</th>
<th>mOS</th>
<th>1y Brain Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRS</td>
<td>64</td>
<td>60</td>
<td>10.4</td>
<td>51</td>
</tr>
<tr>
<td>SRS + WBRT</td>
<td>92</td>
<td>95</td>
<td>7.4</td>
<td>85</td>
</tr>
</tbody>
</table>

p<0.001  p=0.92  p<0.001

Brown JAMA 316, 2016
Brain Metastases – Treatment Options

• Surgery
• WBRT
• WBRT + Surgery
• WBRT + SRS
• SRS

Question: Can we do SRS to resection cavity rather than WBRT following surgery?
RTOG 1270/NCCTG N107C

N107C
SRS vs. WBRT Resected Brain Mets

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

RANDOMIZE

SRS Surgical Bed + SRS unresected mets
WBRT* + SRS unresected mets

*37.5 Gy/15

Fig. 4. Intergroup trial N107C schema.
N107C – WBRT vs. SRS Following Resection

- n=194

- Primary Endpoints:
  - Cognitive Deterioration Free Survival
    - 1 SD Drop in at least 1 cognitive test
  - OS

Brown ASTRO 2016
N107C – WBRT vs. SRS Following Resection

No difference in OS

Worse Cognition with WBRT

Therefore a Positive Trial

Worse LC with SRS

1y LC: 78% vs. 56%

Brown ASTRO 2016
N107C – WBRT vs. SRS Following Resection

SRS Doses:

• 20 Gy <4.2 cc
• 18 Gy 4.2 to <8.0 cc
• 17 Gy 8.0 to <14.4 cc
• 15 Gy 14.4 to <20 cc
• 14 Gy 20 to <30 cc
• 12 Gy 30 cc to 5 cm

Brown ASTRO 2016
Brain Metastases – Treatment Options

• Question: Are there ways to improve the cognitive outcomes of WBRT?

• Memantine

• Hippocampal Avoidance WBRT
RTOG 0614 WBRT + Memantine

- n=508
- WBRT (37.5 Gy) + placebo
- WBRT (37.5 Gy) + Memantine x 6 months

- Primary: HVLT-R DR at 6 months
- Tests:
  - Memory (Hopkins Verbal Learning Test-Revised [HVLT-R])
  - Processing speed (Trail Making Test Part A [TMT-A])
  - Executive function (Trail Making Test Part B [TMT-B])
  - Verbal fluency (Controlled Oral Word Association [COWA])
  - MMSE

Brown Neuro-Onc 15, 2013
RTOG 0614 WBRT + Memantine

• OS: 7 v 8 m (p=0.28)

• Only 149 analyzable pts (29%) at 6 months
  – 442 (80%) expected

• HVLT-R DR better with Memantine, but p=0.059

Brown Neuro-Onc 15, 2013
RTOG 0614 WBRT + Memantine

Cognitive Function Failure = Failure in any of the tests

Brown Neuro-Onc 15, 2013
RTOG 0933: Hippocampal Avoidance WBRT (HA-WBRT)

- Single arm phase II
- n=113 with HA-WBRT (30 Gy in 10)
  - Hippo+5mm: 100% < 9 Gy, Dmax <16 Gy

- Primary endpoint: Mean Relative Decline in HVLT-DR at 4 months compared to baseline
  - Compared to historical WBRT alone (Li JCO 25, 2007)

- HA-WBRT: 7% decline in 0933
- WBRT: 30% decline (historical control)

Gondi JCO 32, 2014
NRG CC001 – WBRT + Memantine +/- Hippocampal Avoidance

- WBRT 30Gy + Memantine x 6 m
- HA-WBRT 30 Gy + Memantine x 6 m

**Primary Objective:**
- Determine if HA-WBRT increases time to neurocognitive decline on: HVLT-R, COWA, TMT A and B.
- Hypothesis: HA-WBRT will increase time to failure at 6 months from 54% to 65%
- 510 accrued over 63 months → 382 evaluable pts
Fig. 5. Spatial isodose distribution for 1 sample patient at the level of the hippocampi for hippocampal avoidance during whole-brain radiotherapy using (a) helical tomotherapy and (b) linear accelerator (LINAC)–based intensity-modulated radiotherapy (IMRT). Grey-shaded region represents the hippocampus. Orange contour represents the hippocampal avoidance region. Green isodose represents 12 Gy; light blue, 27 Gy; pink, 29 Gy; yellow, 30 Gy; red, 38 Gy, in 10 fractions. Representative axial, sagittal, and coronal images are provided.
Brain Metastases – Treatment Options

• Are there patients that should not get radiotherapy?
QUARTZ: WBRT vs. Supportive Care

- n=538
- NSCLC metastases, ‘not suitable for SRS or surgery’
- Endpoint: QALYs (Quality Adjusted Life Years)
  - From Overall Survival (OS) and weekly EQ-5D QOL questionnaire
  - Supportive Care not inferior if \( \leq 7 \) QALY days worse than WBRT

<table>
<thead>
<tr>
<th></th>
<th>Mean QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBRT (20 Gy in 5)</td>
<td>9.2 weeks</td>
</tr>
<tr>
<td>Supportive Care</td>
<td>8.5 weeks</td>
</tr>
</tbody>
</table>

\[
\text{Conclusion: Although did not meet non-inferiority, WBRT little clinical benefit in this group}
\]

Mulvenna Lancet 388, 2016
Langley Clin Onc 25 2013
QUARTZ: WBRT vs. Supportive Care

- Concerns: ‘not suitable for SRS or surgery’
  - 16% GPA 3.5-4.0
  - 45% without extracranial metastases
  - 62% with KPS >70
  - 30% solitary metastasis
  - 83% with newly diagnosed brain mets
  - Median age 66

Mulvenna Lancet 388, 2016
Langley Clin Onc 25 2013
Outline

• Glioma Molecular Overview
• Grade IV – Glioblastoma
• Grade II and III Gliomas – Oligos and Astros
• Brain Metastases

• Benign and Misc. Tumors
Pituitary Adenoma
Pituitary Adenoma: Non-functioning
Constants in the XRT Literature

• No dose response above 45 Gy
  (typically 54 Gy for functioning adenomas)
• LC 90+% for non-functioning
• ~1% vision toxicity
• ~1% secondary malignancy
## Pituitary Adenoma: Non-Functioning

<table>
<thead>
<tr>
<th>Citation</th>
<th>Number</th>
<th>Dose (Gy)</th>
<th>Local Control (%)</th>
<th>Vision Loss</th>
<th>Secondary Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsang IJROBP 30, 1994</td>
<td>128</td>
<td>45</td>
<td>91 at 10 y</td>
<td>NR</td>
<td>1.6%</td>
</tr>
<tr>
<td>Van den Bergh IJROBP 67, 2007</td>
<td>122</td>
<td>45</td>
<td>95 at 10 y</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>McCord IJROBP 39, 1997</td>
<td>141</td>
<td>45</td>
<td>95 at 10 y</td>
<td>NR</td>
<td>1.4%</td>
</tr>
<tr>
<td>Snead IJROBP 71, 2008</td>
<td>100</td>
<td>45</td>
<td>98 at 10 y</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Erridge Rad Onc 93, 2009</td>
<td>385</td>
<td>45</td>
<td>96 at 20 y</td>
<td>1%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
Pituitary Adenomas: General Treatment Schema

• Observation vs. Surgery

• Surgery 1st
  – trans-sphenoidal resection usually
  – Prolactinomas – often medications 1st

• If GTR: No RT

• If STR: Observe vs. RT/SRS
  – RT – if functioning/secretory
  – RT – if ultimate growth would impact function (vision)
  – RT – if ultimate growth would compromise treatment options (SRS now vs. EBRT later)
  – Otherwise can observe a STR (i.e., salvage RT has the same LC as immediate PORT)
Meningioma: General Treatment Schema

• Observation vs. Treatment (Surgery or RT/SRS)

• Grade I: If GTR: No RT
   If STR: Observe vs. RT
   RT – if ultimate growth would impact function (vision)
   RT – if ultimate growth would compromise treatment options
   (i.e., SRS now vs. EBRT later)
   Otherwise can observe a STR
   (i.e., salvage RT has the same LC as immediate PORT*)

• Grade II: If GTR: Controversial on role of RT vs observation
   If STR: RT

• Grade III: RT regardless of extent of resection

*Controversial – see next slide
Meningioma Overview

• See Stephanie Weiss’s thoughtful talk from ASTRO 2016
  – Recurrent grade 1 may be more aggressive
  – Therefore adjuvant treatment may be better than salvage
# Meningioma: Simpson’s Grade

**n = 265 pts**  
1928-1954

<table>
<thead>
<tr>
<th>GRADE</th>
<th>DEFINITION OF EXTENT OF RESECTION</th>
<th>10 y LF</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Gross total resection of tumor, dural attachments and abnormal bone</td>
<td>10%</td>
</tr>
<tr>
<td>II</td>
<td>Gross total resection of tumor, coagulation of dural attachments</td>
<td>20%</td>
</tr>
<tr>
<td>III</td>
<td>Gross total resection of tumor without resection or coagulation of dural attachments, or extradural extensions (e.g. invaded or hyperostotic bone)</td>
<td>30%</td>
</tr>
<tr>
<td>IV</td>
<td>Partial resection of tumor</td>
<td>44%</td>
</tr>
<tr>
<td>V</td>
<td>Simple decompression (biopsy)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Simpson, J Neurol Neurosurg Psychiat 20, 1957
RTOG 0539 – Phase II Meningioma

• Low Risk: Grade I: GTR (Simpson I-III)
  STR (Simpson IV-V)

• Intermediate: Grade I: Recurrent
  Grade II: GTR

• High Risk: Grade II: Recurrent
  STR
  Grade III: new, recurrent, GTR, STR
RTOG 0539 – Phase II Meningioma

- Low Risk: Observation
- Intermediate: 54 Gy to GTV + 1.0 cm CTV + 0.3-0.5 cm PTV
  - CTV may be reduced to 0.5 cm at natural barriers
- High Risk: 54 Gy to GTV + 2.0 cm CTV + 0.3-0.5 cm PTV
  60 Gy to GTV + 1.0 cm CTV

No edema or dural tail included in GTV

<table>
<thead>
<tr>
<th>Critical Structure</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenses</td>
<td>5 Gy</td>
<td>7 Gy</td>
</tr>
<tr>
<td>Retinae</td>
<td>45 Gy</td>
<td>50 Gy</td>
</tr>
<tr>
<td>Optic Nerves</td>
<td>50 Gy</td>
<td>55 Gy</td>
</tr>
<tr>
<td>Optic Chiasm</td>
<td>54 Gy</td>
<td>56 Gy</td>
</tr>
<tr>
<td>Brainstem</td>
<td>55 Gy</td>
<td>60 Gy</td>
</tr>
</tbody>
</table>
Pilocytic Astrocytoma

- Grade 1 tumors, generally pediatric
- 10 y OS >80% with surgery\(^1\)
- Prospective trial in 20 adults\(^2\)
  - GTR or STR $\rightarrow$ Observation
  - Biopsy + 50.4 Gy

Conclusions:
After STR or GTR $\rightarrow$ can observe
Do RT if progression or if significant residual disease that may impact function if it were to grow

Ependymoma

- Pediatrics: 90% intracranial
- Adults: 75% spinal

- Grade I: Subependymoma
  Myxopapillary Ependymoma (arise in conus)
- Grade II: Ependymoma
- Grade III: Anaplastic Ependymoma

- Formerly Grade IV Ependymoblastoma → now PNET (ETANTR - embryonal tumors with abundant neuropil and true rosettes)
Ependymoma: Spinal

- Spinal Ependymoma\textsuperscript{1,2}: GTR $\rightarrow$ Observe
  STR $\rightarrow$ RT

1. Abdel-Wahab IJROBP 64, 2006
2. Volpp IJROBP 69, 2007
Ependymoma: Spinal Myxopapillary Ependymoma

- Role of Post-Op Radiotherapy (PORT) controversial:
  - If STR → PORT
    - Doses ≥50.4 Gy appear better than <50.4 Gy\(^1,3\)
  - If GTR:
    - Data overall suggests improved PFS with immediate PORT
    - But, after GTR, observation is an option, as it appears that salvage RT has similar LC as adjuvant RT\(^1,2\)
      - 79-100% salvage of failures\(^1,2\)

1. Pica IJROBP 74, 2009  
2. Chao JNSpine 14, 2011  
Ependymoma: Intracranial

- Historically, all get PORT (I use 59.4 Gy, GTV +1cm, per Merchant\(^1\))
- If GTR:
  - Supratentorial: consider observation (similar to spinal)
    - However, in pediatrics, poor 5 y EFS of only 61\(^%\)\(^2\) (ACNS0121 trial)
  - Infratentorial: all need PORT\(^3\)
- If STR:
  - Consider chemo → 2\(^{nd}\) look surgery\(^2\)
  - PORT
- If grade III → PORT
- CSI only if CSF positive (even for grade III)\(^4\)

<table>
<thead>
<tr>
<th>N=45 posterior-fossa(^3)</th>
<th>10 year Local Control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTR + PORT</td>
<td>100</td>
</tr>
<tr>
<td>GTR</td>
<td>50</td>
</tr>
<tr>
<td>STR + PORT</td>
<td>36</td>
</tr>
</tbody>
</table>

Summary – Standard of Care

- GBM - Stupp NEJM 2005 and Stupp JAMA 2015
- Oligodendrogliomas - RTOG 9402 and EORTC 26951 - 2012
- Low Grade Gliomas - RTOG 9802 (not yet published)
- Brain Metastases - Many. Await RTOG 1270/NCCTG N107C
  Await NRG HA-WBRT trials