Central Nervous System: Notable Developments in the Management of Primary and Recurrent Gliomas

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Objectives

• Background
• Describe how to evaluate patient and disease characteristics to determine the most appropriate adjuvant therapy options for individuals with:
  – Primary low-grade gliomas
  – Anaplastic oligodendrogliomas
  – Primary glioblastomas
• Case examples, evidence, NCCN recommendations
Glioma: Significance and Impact

- Median age at diagnosis: 56 years
- Incidence: Men > Women; Caucasians > African Americans
- Standard treatment: surgery, radiation, chemotherapy
  - Median overall survival (OS): 17 months from diagnosis
- Rated high on years of life lost due to cancer
  - Measure of burden of disease on patients
  - UK: #1 of 17 cancer sites
  - US: #7 of 22 cancer sites
- Leading cause of cancer death for children and young adults
  - Second leading cause of cancer death for young men age 20-40
  - Second most common malignancy of children, leading solid cancer and leading cause of cancer death in children
- Public health cost of disease and treatment among highest in oncology
  - Projections of the Cost of Cancer Care in the United States: 2010-2020, ranks brain cancer as the most expensive in terms of annualized net cost for care per patient ($140,000 for initial care)


Etiology of Brain Cancer

- No lifestyle exposure is linked to glioma susceptibility in adults
- Ionizing radiation in children
- GWAS (genome wide association studies) identified susceptibility loci for glioma
  - 8q24.21 → CCDC26 - modulates death and differentiation
  - 5p15.33 → TERT - component of telomerase
  - 9p21.3 → CDKN2A-CDKN2B - tumor suppressor gene - increases risk
  - 20q13.33 → RTEL1 - genomic stability
  - 11q23.3 → PHLDB1
  - 7p11.2 → EGFR
- Risk related to genetic susceptibility

Case Presentation

2005

2015

• 31-year-old male with remote history of concussion 2005
• New onset partial seizure in 2015
• Exam nonfocal
• MRI obtained

Case Presentation

H&E 10X H&E 40X

GFAP IDH1 R132H

Post-op Neuropathology

GFAP, glial fibrillary acidic protein; H&E, hematoxylin and eosin; IDH1, isocitrate dehydrogenase-1
Audience Polling Results

Question

The optimal treatment recommendations for this patient is:
1. Radiation therapy alone
2. PCV chemotherapy
3. Temozolomide chemotherapy
4. Radiation therapy followed by PCV

28% 32% 12% 27%

Glioma Grading and Natural History

Median Survival (Range)

Astrocytoma
- Grade I: >10 years
  - Benign histopathological features
  - Pilocytic astrocytoma (PA), pleomorphic xanthoastrocytomas (PXA), subependymal giant cell astrocytomas (SEGA)
- Grade II: 5 years (3-10 years)
  - Nuclear atypia
- Grade III: 3 years
  - Nuclear atypia + mitosis
- Grade IV: 1 year
  - Nuclear atypia
  - Mitosis
  - Endothelial proliferation and/or necrosis

Oligodendrogloma
- Low Grade: 15 years (8-20 years)
  - 1p/19q co-deletion: 2 years more
- Grade III: 5 years
  - 1p/19q co-deletion: 7 years
  - Without 1p/19q codeletion: 3 years

Low-Grade Gliomas
WHO Grade II

- This includes astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas
- Most commonly occur in children and young adults; biphasic age distribution
  - 1st peak around ages 6-12 years
  - 2nd peak between 3rd and 5th decades
- Between 50–80% present with seizure depending on location
- They are called “low-grade” but they are NOT benign
  - Median OS is around 6.5–8 years
- Very heterogeneous group with varying clinical behavior
  - Good prognostic signs include: age <40 years, seizures at presentation and no additional neurological deficits, KPS ≥70, MMSE >26/30
  - Poor prognostic signs include: tumor diameter >5–6 cm and the presence of contrast enhancement

KPS, Karnofsky performance status; MMSE, mini mental state examination

Treatment of Low-grade Gliomas (LGG)

- Standard treatment options for diffuse astrocytomas (WHO grade II) include the following:
  - Surgery alone
  - Surgery followed by radiation therapy
  - Surgery followed by chemotherapy
  - Surgery followed by radiation therapy and chemotherapy
- Controversy exists about the timing of radiation therapy after surgery
Phase III study of radiation therapy with or without procarbazine, CCNU, and vincristine (PCV) in low grade glioma. RTOG 9802 with Alliance, ECOG and SWOG


Mayo Clinic, MN; NRG Oncology Statistics and Data Management Center, Philadelphia, PA; Wake Forest University; NC; MD Anderson Cancer Center, TX; Wayne State University, MI; Barrow Neurological Institute, AZ; Radiology Imaging Associates, Englewood, CO; Triangle Neurosurgeons, Raleigh, NC; MD Anderson Cancer Center, TX; Mid-Columbia Medical Center, The Dalles, OR; Arizona Oncology Services Foundation, Phoenix, AZ; Cleveland Clinic, OH; Medical College of Wisconsin, WI; Centre Hospitalier de l’Universite de Montreal, QB; London Regional Cancer Program, London, ON; Wayne State University, MI; Cross Cancer Institute, Edmonton, AB; Emory University, GA; University of Maryland, MD


LOW RISK
Age <40 AND GROSS TOTAL RESECTION

HIGH RISK
Age ≥40 OR SUBTOTAL RESECTION/BIOPSY

Arm 1 = Observe

Arm 2 = Radiation Therapy (54 Gy/30 fractions)

Arm 3 = Radiation Therapy PCV x 6 cycles
• CCNU 110 mg/m² (day 1)
• Procarbazine 60 mg/m² (days 8-21)
• Vincristine 1.4 mg/m² (days 8 & 29)
(2.0 mg cap)

Randomize

Stratify by:
Oligo-dominant versus Astro-dominant;
KPS;
Age;
Enhancement

Balanced for demographics, histology, surgery, and functional status


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ASCO 2014: Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>RT Alone</th>
<th>RT + PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>4.0 years</td>
<td>10.4 years</td>
</tr>
<tr>
<td>5-year</td>
<td>44.1%</td>
<td>61.2%</td>
</tr>
<tr>
<td>10-year</td>
<td>20.9%</td>
<td>50.5%</td>
</tr>
</tbody>
</table>

PCV, procarbazine, lomustine, and vincristine.
ASCO 2014: Overall Survival

<table>
<thead>
<tr>
<th>Patients at Risk</th>
<th>Years after Randomization</th>
<th>Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT alone</td>
<td>126</td>
<td>109</td>
</tr>
<tr>
<td>RT + PCV</td>
<td>125</td>
<td>105</td>
</tr>
</tbody>
</table>

p = 0.03 (Wilcoxon)  
p = 0.002 (Log-rank)  
HR = 0.59

PCV, procarbazine, lomustine, and vincristine.

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Overall Survival
ASCO 2014

<table>
<thead>
<tr>
<th></th>
<th>RT Alone</th>
<th>RT + PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>7.8 years</td>
<td>13.3 years</td>
</tr>
<tr>
<td>5-year</td>
<td>63.1 %</td>
<td>72.3 %</td>
</tr>
<tr>
<td>10-year</td>
<td>40.1 %</td>
<td>60.1 %</td>
</tr>
</tbody>
</table>

PCV, procarbazine, lomustine, and vincristine.
### Hematologic Toxicity

<table>
<thead>
<tr>
<th>Blood/Bone Marrow</th>
<th>RT Alone (n=126)</th>
<th>RT+PCV (n=125)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Packed RBC transfusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection NOS</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Similar for GI and constitutional

PCV, procarbazine, lomustine, and vincristine.

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### Conclusions (Survival)

- For patients with grade II glioma with less than gross total tumor resection or who are >40 years of age, RT + PCV prolongs both progression-free and overall survival compared with RT alone
  - Median survival is increased by 5.5 years
  - Five-year and 10-year survival are increased by 9% and 20%, respectively
  - First prospective study ever to demonstrate a treatment-related increase in survival in patients with grade II glioma

PCV, procarbazine, lomustine, and vincristine.
Conclusions (Toxicity)

- Toxicity, though greater with PCV, is acceptable, and similar to that seen with many combination chemotherapy regimens commonly in use.

- Severe cognitive impairment at 5 years, as measured by MMSE, is infrequent. Longer term or less severe cognitive decline cannot be assessed.

MMSE, mini mental state examination; PCV, procarbazine, lomustine, and vincristine.

Molecular Diagnostics of Low Grade Gliomas

- Ki-67 expression is typically less than 10% in low grade gliomas (LGGs)
- p53 mutations are common in low-grade astrocytomas but rare in oligodendrogliomas
- The majority of oligodendrogliomas have 1p/19q chromosome losses
- Most LGGs have a mutation in IDH (isocitrate dehydrogenase, an enzyme in the Krebs cycle)
- 3 molecular categories of LGGs:
  1. 1p/19q codeletion and IDH mutation
  2. IDH mutation and no 1p/19q codeletion
  3. Neither IDH mutation nor 1p/19q codeletion

Key Points and Implications for Patient Care

- Important role for surgical resection
- Observation for gross total resection – Age cut off?
- Radiation therapy alone is not adequate for high-risk low-grade glioma
- Chemotherapy considerations
Anaplastic Oligodendroglioma (AO)

- Oligodendrogliomas account for ~5% of adult brain tumors\(^1\)
- AO classified as WHO Grade III
- Distinct histologic appearance
  - “Fried egg” cell morphology
  - “Chicken wire” capillary network
- Combined allelic loss of chromosomes 1p and 19q:
  - Found in 60-70% of anaplastic tumors
  - Associated with longer survival and greater chemosensitivity (Cairncross et al\(^2\))
  - Often results from unbalanced translocation of chromosome 1 and 19 → loss of short arm (q) of 1, long arm (p) of 19 (Jenkins et al\(^3\))
- Mutations in CIC and FUBP1 genes found in some cases of AO with 1p 19q loss\(^4\)


Audience Polling Results

**Question**

The optimal treatment recommendations for anaplastic oligodendroglioma is:

1. Radiation therapy alone
2. PCV chemotherapy
3. Temozolomide chemotherapy
4. Radiation therapy followed by PCV

82%
Anaplastic Gliomas: Results

**RTOG 9402**
- Number of cycles of PCV (max=4)
  - Median: 4
  - 4 cycles in 54%
  - Early stopping
    - Toxicity: 20%
    - Tumor progression: 14%
- PCV Toxicity
  - 94 (64%) patients with grade 3-5 toxicity
- Salvage treatment
  - Salvage chemotherapy more common with RT only arm
    - (41 vs 75%, P<.001; codeleted subset: 57 vs 81%, P=.04)

**EORTC 26951**
- Number of cycles of PCV (max=6)
  - Median: 3
  - 6 cycles in 30%
  - Early stopping
    - Toxicity: 38%
    - Tumor progression: 24%
- PCV Toxicity
  - 74 (46%) with grade 3-4 hematological toxicity
- Salvage treatment
  - Salvage chemotherapy more common in RT only arm
    - (53 vs 75%)


Current Results: 1p 19q Co-deleted Anaplastic Gliomas

- Overall Survival
  - HR: 0.56, 95% CI [0.31, 1.03]

RTOG 9402
- Median Survival
  - PCV + RT: 14.7 years
  - RT alone: 7.3 years

EORTC 26951

ANAPLASTIC GLIOMAS PATHOLOGY

1p19q codeleted: Anaplastic oligodendroglioma

Anaplastic oligoastrocytoma

1p19q uni- or non-deleted: Anaplastic oligodendroglioma

Anaplastic oligoastrocytoma

Anaplastic astrocytoma

Anaplastic gliomas Poor Performance status (KPS <60)

ADJUVANT TREATMENT

Fractionated external beam RT and 
neoadjuvant or adjuvant PCV 
chemotherapy (category 1)
or
Fractionated external beam RT and 
temozolomide chemotherapy 
or
PCV or temozolomide chemotherapy 
(category 2B)

FOLLOW-UP

MRI 2–6 wks after RT, 
them every 2–4 mo for 2–3 y, then less 
frequently

Key Points and Implications for Patient Care

• Radiation therapy alone is no longer adequate 
for patients with anaplastic oligodendroglioma 
with 1p 19q co-deletion.

• Existing data support first-line treatment with 
radiation and chemotherapy
  – The optimal treatment paradigm has not been 
established
  – Chemo → RT
  – RT → Chemo
  – Temozolomide vs. PCV

• CODEL (NCT00887146) and CATNON NCI 
(NCT00626990) Cooperative trials
Malignant Gliomas

**Anaplastic Astrocytoma**
- Grade III malignant glioma
- Less aggressive than glioblastoma multiforme, with somewhat better prognosis
- Frequency highest in children and young adults (age 30–40 years)
- Often recurs as higher-grade tumor
- Median survival 36–48 months

**Glioblastoma Multiforme**
- Most aggressive, difficult to treat primary brain tumor
- Histology:
  - Grade IV, poorly differentiated
  - Necrosis, vascular endothelial hyperplasia, frequent mitoses, cellular atypia
  - Neovascularization and pseudopallisading
- Most common in older adults: peak age 55–65 years
- Rapid growth; size may double every 10 days


Clinical and Molecular Genetic features of Patients with Primary and Secondary Glioblastoma Multiforme Determined from a Recent Population-based Study

- Indicates genetic alterations that are significantly different in the frequency between primary and secondary glioblastoma multiform tumors

Case Presentation

History and Physical

- 64-year-old male with a 2-week history of slurring speech with worsening headache
- Prior medical history: mild hypertension
- Social history: retired school administrator, no tobacco
- Physical exam was normal; neurological exam revealed dysarthria

Imaging

Pre-Op

Post-Op
Neuropathology

Mitotic figures

MIB-1 (anti-Ki67)

Necrosis

Question

• The optimal treatment recommended for this patient is:
  1. Radiation therapy alone
  2. Temozolomide chemotherapy
  3. Temozolomide chemotherapy and RT
  4. Radiation therapy followed by PCV

PCV, procarbazine, lomustine, and vincristine.
**Question**

The optimal treatment recommended for this patient is:

1. Radiation therapy alone
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3. Temozolomide chemotherapy and RT
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**Audience Polling Results**

**EORTC 26981-22981: Phase III Randomized Trial in Newly-Diagnosed Resected Glioblastoma**

**Table 3. Overall and Progression-free Survival According to Treatment Group.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Radiotherapy (N=286)</th>
<th>Radiotherapy plus Temozolomide (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival (mo)</td>
<td>12.1 (11.2–13.0)</td>
<td>14.6 (13.2–16.8)</td>
</tr>
<tr>
<td>Overall survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>84.2 (80.0–88.5)</td>
<td>86.3 (82.3–90.3)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>50.6 (44.7–56.4)</td>
<td>61.1 (55.4–66.7)</td>
</tr>
<tr>
<td>At 18 months</td>
<td>20.9 (16.2–26.6)</td>
<td>39.4 (33.8–45.1)</td>
</tr>
<tr>
<td>At 24 months</td>
<td>10.4 (6.8–14.1)</td>
<td>26.5 (21.2–31.7)</td>
</tr>
<tr>
<td>Median progression-free survival (mo)</td>
<td>5.0 (4.2–5.5)</td>
<td>6.9 (5.8–8.2)</td>
</tr>
<tr>
<td>Progression-free survival (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 months</td>
<td>36.4 (30.8–41.9)</td>
<td>53.9 (48.1–59.6)</td>
</tr>
<tr>
<td>At 12 months</td>
<td>9.1 (5.8–12.4)</td>
<td>26.9 (21.8–32.1)</td>
</tr>
<tr>
<td>At 18 months</td>
<td>3.9 (1.6–6.1)</td>
<td>18.4 (13.9–22.9)</td>
</tr>
<tr>
<td>At 24 months</td>
<td>1.5 (0.1–3.0)</td>
<td>10.7 (7.0–14.3)</td>
</tr>
</tbody>
</table>

Inactivation of the Methylguanine Methyltransferase (MGMT) by Promoter Methylation

Normal tissue DNA → MGMT → Repairs DNA damage, including damage induced by TMZ; tissue is resistant to TMZ

Tumor DNA → MGMT → Unable to repair DNA damage induced by TMZ; tumor cell death in response to TMZ

EORTC 26981-22981: MGMT Promoter Status and Survival

<table>
<thead>
<tr>
<th>Promoter Status and Outcome</th>
<th>Radiotherapy (N=100)</th>
<th>Temozolomide plus Radiotherapy (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylated MGMT promoter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>46</td>
<td>46</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mos)</td>
<td>5.9 (3.3–7.7)</td>
<td>10.3 (6.1–14.0)</td>
</tr>
<tr>
<td>Rate at 5 mos (%)</td>
<td>47.0 (30.4–62.3)</td>
<td>66.5 (55.4–82.4)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.90</td>
<td>0.48 (0.31–0.74)</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mos)</td>
<td>15.3 (13.0–20.9)</td>
<td>21.7 (17.4–30.4)</td>
</tr>
<tr>
<td>Rate at 2 yrs (%)</td>
<td>22.7 (16.2–30.3)</td>
<td>48.6 (35.2–66.6)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.90</td>
<td>0.51 (0.31–0.84)</td>
</tr>
<tr>
<td>Methylated MGMT promoter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>54</td>
<td>60</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mos)</td>
<td>4.4 (3.1–6.9)</td>
<td>5.3 (3.8–7.8)</td>
</tr>
<tr>
<td>Rate at 5 mos (%)</td>
<td>35.2 (22.5–47.9)</td>
<td>46.0 (27.5–52.4)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.90</td>
<td>0.62 (0.31–0.86)</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median duration (mos)</td>
<td>13.8 (11.0–14.4)</td>
<td>12.7 (11.5–14.6)</td>
</tr>
<tr>
<td>Rate at 2 yrs (%)</td>
<td>&lt;27</td>
<td>13.8 (11.5–14.6)</td>
</tr>
<tr>
<td>Hazard ratio for death</td>
<td>1.90</td>
<td>0.63 (0.47–1.02)</td>
</tr>
</tbody>
</table>

Clinical Trials

- **Alliance A071102 (NCT02152982):** A Phase II/III Randomized Trial of Veliparib or Placebo in Combination With Adjuvant Temozolomide in Newly Diagnosed Glioblastoma With MGMT Promoter Hypermethylation

- **CheckMate 498 (NCT02617589):** A Randomized Phase III Open Label Study of Nivolumab vs. Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor 06-methylguanine DNA methyltransferase) Glioblastoma

Elderly

- **Wick et al, Lancet Oncology 13(7):707-715, 2012**
  German Neuro-oncology working group

- **Malmstrom et al, Lancet Oncology 13(9):916-926, 2012 Phase III Nordic trial**
**Tumor Treating Fields – An entirely novel modality for antimitotic therapy**

**EF14 Phase III Trial in Newly-Diagnosed Resected Glioblastoma: Study Design**

- **Max 7 weeks**
- **Tumor Treating Fields**
  - >18 hours/day until 2nd progression
  - (or maximum of 24 months)
- until 2nd progression

**Concomitant**
- **RT + TMZ**

**Stratification:**
- Extent resection (complete versus partial versus biopsy)
- MGMT methylation status

**Adjuvant**
- **TMZ**

**EF14 Trial Results**

**Progression-free Survival**  
(Primary endpoint, ITT population)

<table>
<thead>
<tr>
<th>TTF + TMZ</th>
<th>TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>7.1 months</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9-8.2 months</td>
</tr>
<tr>
<td>Log Rank</td>
<td>P = .001</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.62</td>
</tr>
</tbody>
</table>

**Overall Survival**  
(Secondary endpoint, ITT population)

<table>
<thead>
<tr>
<th>TTF + TMZ</th>
<th>TMZ</th>
</tr>
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<tbody>
<tr>
<td>Median</td>
<td>19.6 months</td>
</tr>
<tr>
<td>95% CI</td>
<td>16.6-24.4 months</td>
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<tr>
<td>Log Rank</td>
<td>P=.03</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.74</td>
</tr>
</tbody>
</table>

TMZ, temozolomide; TTF, tumor treating fields.  

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**Glioblastoma Pathology**

- **Age ≤70 y**
  - Good performance status (KPS ≥80)
  - Poor performance status (KPS <80)
  - Glioblastoma ± carmustine (BCNU) wafer

- **Age >70 y**
  - Good performance status (KPS ≥80)
  - Poor performance status (KPS <80)

**Adjuvant Treatment**

- Standard focal brain RT + concurrent and adjuvant temozolomide (category 1)
- Standard or hypofractionated focal brain RT or Temozolomide or Palliative/Best supportive care
- Hypofractionated focal brain RT alone (category 1) or Standard focal brain RT + concurrent and adjuvant temozolomide or Hypofractionated focal brain RT + concurrent and adjuvant temozolomide or Temozolomide

**Follow-up**

- MRI 2–6 wk after RT, then every 2–4 mo for 2–3 y, then less frequently

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Key Points and Implications for Patient Care

- Clinical trials for newly-diagnosed glioblastoma demonstrate increasing role for MGMT methylation status in treatment selection
- Elderly and/or low performance status patients: treatment guided by MGMT methylation status
- Consideration of Tumor Treating Fields therapy (TTF) for highly selected patients

MGMT, methylguanine methyl-transferase

Summary

- Low grade glioma
  - Role of radiation and chemotherapy
  - Prognostic impact of molecular diagnostics
- Anaplastic Oligodendroglioma (AO)
  - Molecular markers for AO
  - Treatment with chemotherapy + RT
- Glioblastoma WHO stage IV
  - MGMT methylation status
  - Elderly and/or low KPS
  - TTF

KPS, Karofsky performance score; MGMT, methylguanine methyl-transferase; TTF, tumor treating fields