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[1]**
- **Incidence: Men > Women; Caucasians > African Americans[1]**
- **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[2]**
  - **US: #7 of 22 cancer sites[3]**
- **Leading cause of cancer death for children and young adults[4]**
  - **Second leading cause of cancer death for young men age 20-40[4]**
  - **Second most common malignancy of children, leading solid cancer and leading cause of cancer death in children[3]**
- **Public health cost of disease and treatment among highest in oncology[5-7]**
  - ***Projections of the Cost of Cancer Care in the United States: 2010-2020*[5], ranks brain cancer as the most expensive in terms of annualized net cost for care per patient ($140,000 for initial care)**

1. Ostrom QT, et al. Neuro Oncol 2015;17 Suppl 4:iv1-iv62; 2. Burnet NG, et al. Br J Cancer 2005;92:241-245; 3. Howlader N, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD; 2015; 4. Siegel RL, et al. CA Cancer J Clin 2015;65:5-29; 5. Mariotto AB, et al. J Natl Cancer Inst 2011;103:117-128; 6. Yabroff KR, et al. J Natl Cancer Inst 2008;100:630-641; 7. Yabroff KR, et al. Cancer Epidemiol Biomarkers Prev 2011;20:2006-2014.

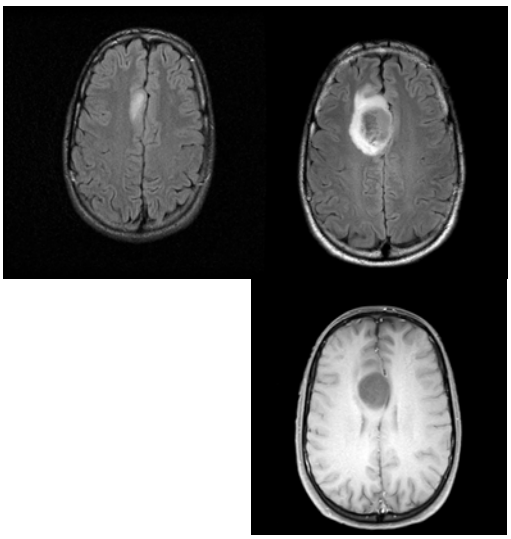
Etiology of Brain Cancer

- No lifestyle exposure is linked to glioma susceptibility in adults
- Ionizing radiation in children
- GWAS (genome wide association studies) identified susceptibility loci for glioma[1,2]
  - 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

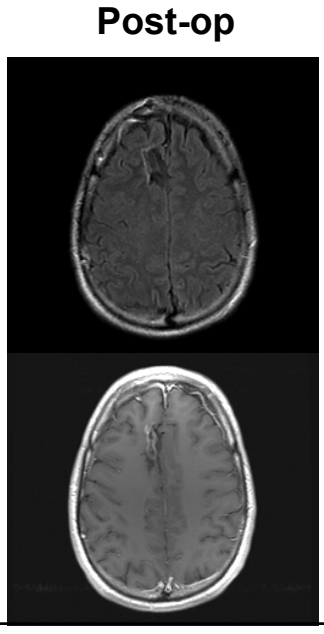
1. Shete S, et al. Nat Genet 2009;41:899-904; 2. Rajaraman P, et al. Hum Genet 2012;131:1877-1888.

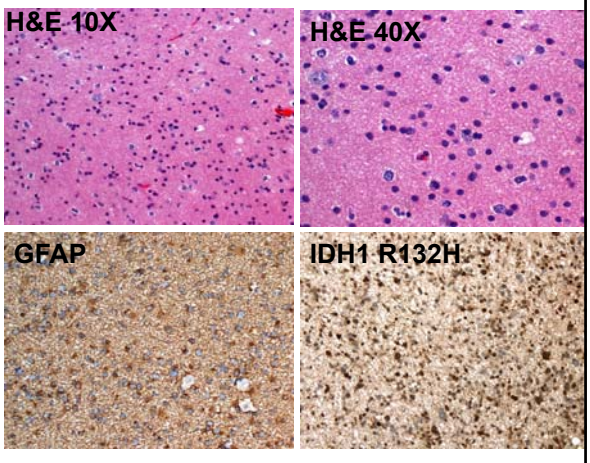
Case Presentation

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



Case Presentation





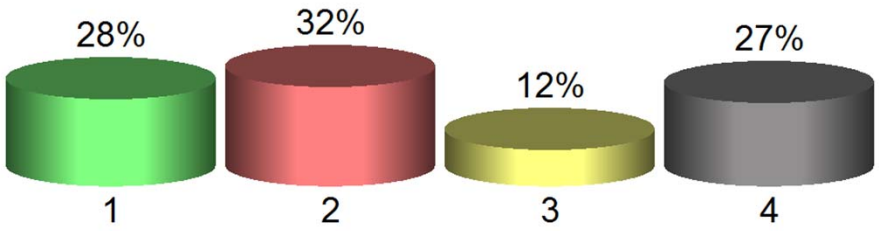
GFAP, glial fibrillary acidic protein; H&E, hematoxylin and eosin; IDH1, isocitrate dehydrogenase-1

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



Glioma Grading and Natural History

Median Survival (Range)

Astrocytoma

- **Grade I: >10 years**
  - **Benign histopathological features**
  - **Pilocytic astrocytoma (PA), pleomorphic xanthroastrocytomas (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**

Oligodendroglioma

- **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**

DeAngelis LM. N Engl J Med 2001;344:114-123.
Van den Bent MJ, et al. Crit Rev Oncol Hematol 2008;66:262-272.

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 heterogenous 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

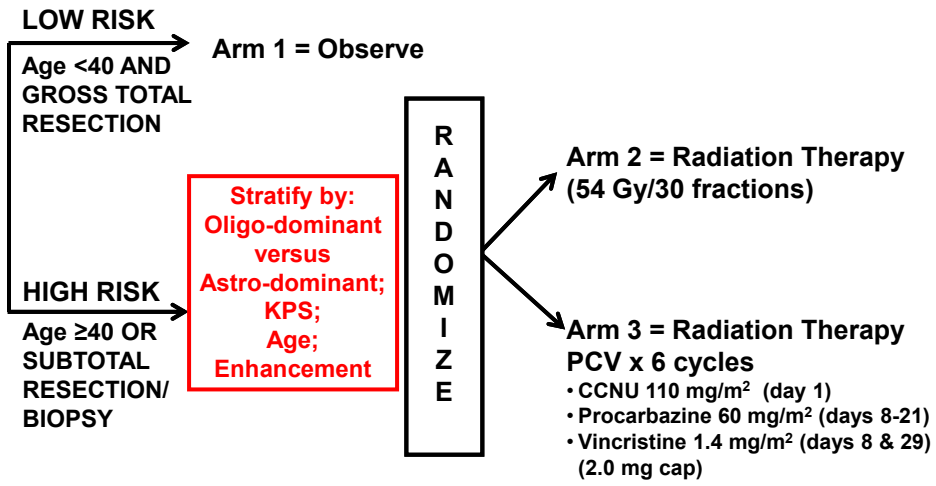
Jan C. Buckner, Stephanie L. Pugh, Edward G. Shaw, Mark R. Gilbert, Geoffrey Barger, Stephen Coons, Peter Ricci, Dennis Bullard, Paul D. Brown, Keith Stelzer, David Brachman, John H. Suh, Christopher J. Schultz, Jean-Paul Bahary, Barbara Jean Fisher, Harold Kim, Albert D. Murtha, Walter J. Curran Jr., Minesh P. Mehta

Mayo Clinic, MN; NRG Oncology Statistics and Data Management Center, Philadephia, 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

CCNU, lomustine.

Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.
Shaw EG, et al. J Clin Oncol 2012;30:3065-3070.

RTOG 9802 Trial Schema

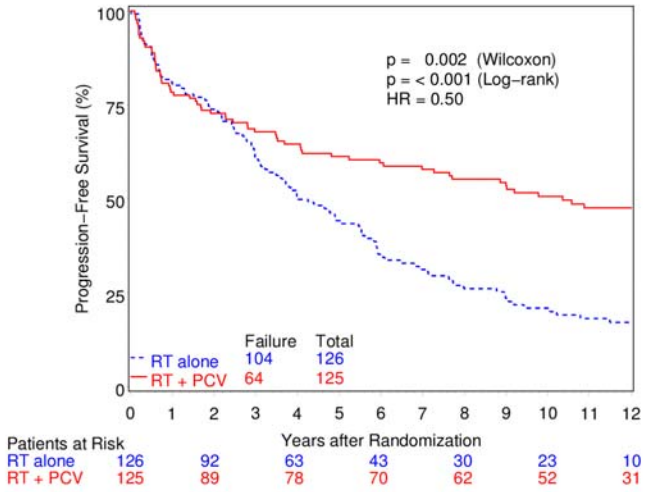


Balanced for demographics, histology, surgery, and functional status

CCNU, lomustine; PCV, procarbazine, lomustine, and vincristine; RTOG, radiation therapy oncology group.

Shaw EG, et al. J Clin Oncol 2012;30:3065-3070; NCT00003375.

ASCO 2014: Progression-Free Survival



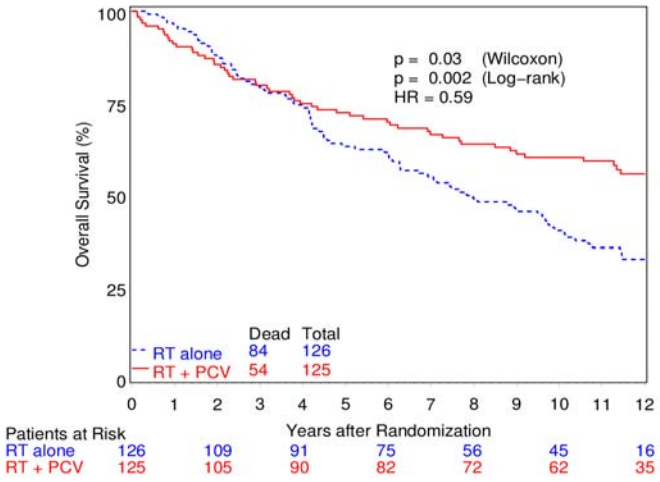
PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

Progression-Free Survival
ASCO 2014

	RT Alone	RT + PCV
Median	4.0 years	10.4 years
5-year	44.1%	61.2%
10-year	20.9%	50.5%

PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

ASCO 2014: Overall Survival



PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

Overall Survival
ASCO 2014

	RT Alone	RT + PCV
Median	**7.8 years**	**13.3 years**
5-year	**63.1 %**	**72.3%**
10-year	**40.1%**	**60.1%**

PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

Hematologic Toxicity

	RT Alone (n=126)					RT+PCV (n=125)				
	Grade					Grade				
	1	2	3	4	5	1	2	3	4	5
Blood/Bone Marrow	2	2	1	0	0	11	20	52	12	0
Hemoglobin decreased	2	0	0	0	0	32	11	5	1	0
Packed RBC transfusion	0	0	0	0	0	1	0	2	0	0
Platelet count decreased	1	1	0	0	0	20	12	23	0	0
Platelet transfusion	0	0	0	0	0	0	0	0	1	0
Neutropenia	0	0	1	0	0	7	11	44	11	0
Febrile neutropenia	0	0	0	0	0	0	1	0	0	0
Infection NOS	0	1	0	0	0	11	15	2	0	0
Lymphopenia	0	1	0	0	0	0	3	1	0	0

Similar for GI and constitutional

PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

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.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.

Conclusions (Toxicity)

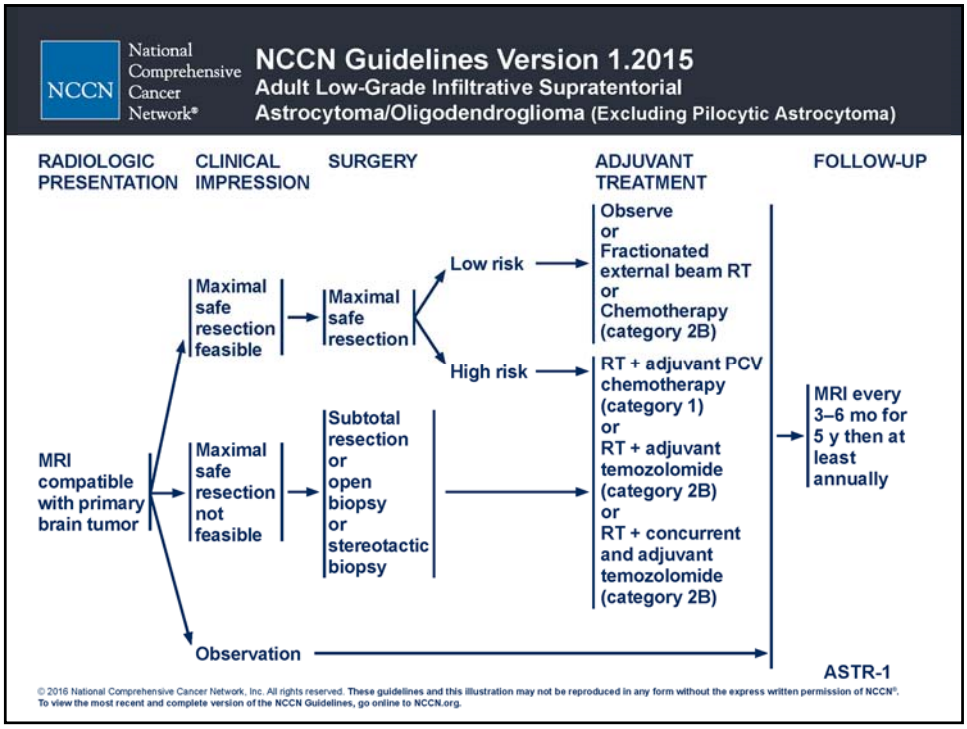
- Toxicity, though greater with PCV, is acceptable, and similar to that seen with many combination chemotherapy regimens commonly in used
- Severe cognitive impairment at 5 years, as measured by MMSE, is infrequent. Longer term or less severe cognitive decline cannot be assessed.

MMSE, mini mental state examination; PCV, procarbazine, lomustine, and vincristine.
Buckner JC, et al. ASCO Meeting Abstracts 2014;32:2000.
Shaw EG, et al. J Clin Oncol 2012;30:3065-3070.

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

The Cancer Genome Atlas Research Network, NEJM 372(26): 2481-2497; June 25, 2015

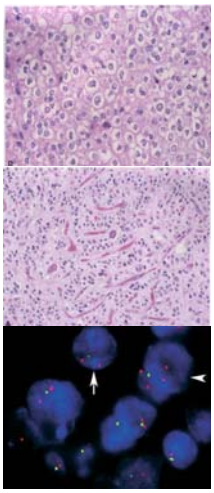


Key Points and Implications for Patient Care

- **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]



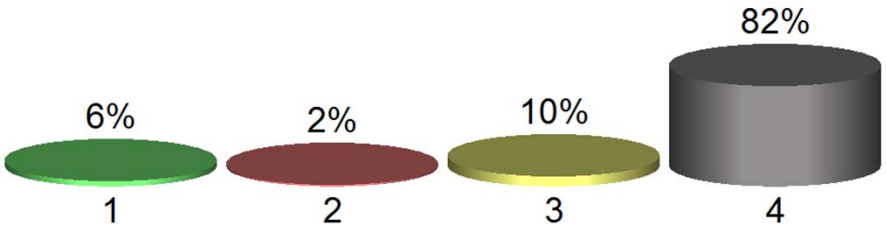
1. Jaeckle KA, Oligodendroglial tumors, Semin Oncol 2014 Aug: 41 (4): 468-477
2. Cairncross JG, et al. J Natl Cancer Inst 1998;90:1473-1479.
3. Jenkins RB, et al. Cancer Res 2006;66:9852-9861.
4. Bettegowda C, et al. Science 2011;333:1453-1455

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



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)

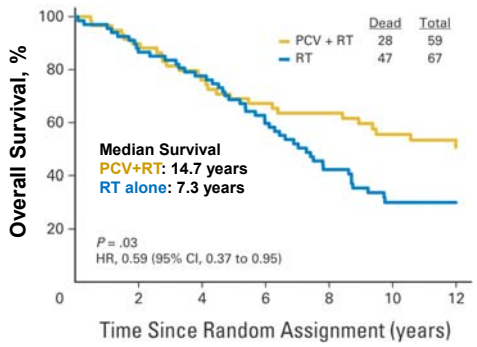
Cairncross G, et al. J Clin Oncol 2006;24:2707-2714.
Cairncross G, et al. J Clin Oncol 2013;31:337-343.

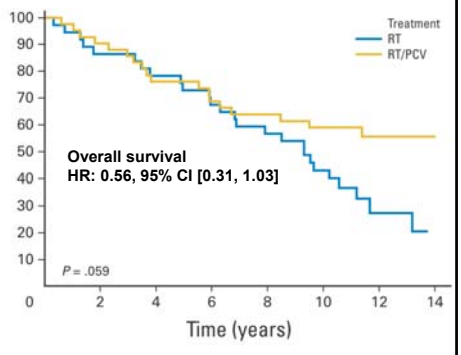
EORTC 26951

- 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%)

van den Bent MJ, et al. J Clin Oncol 2006;24:2715-2722.
van den Bent MJ, et al. J Clin Oncol 2013;31:344-350.

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





RTOG 9402

EORTC 26951

Cairncross G, et al. J Clin Oncol 2013;31:337-343.

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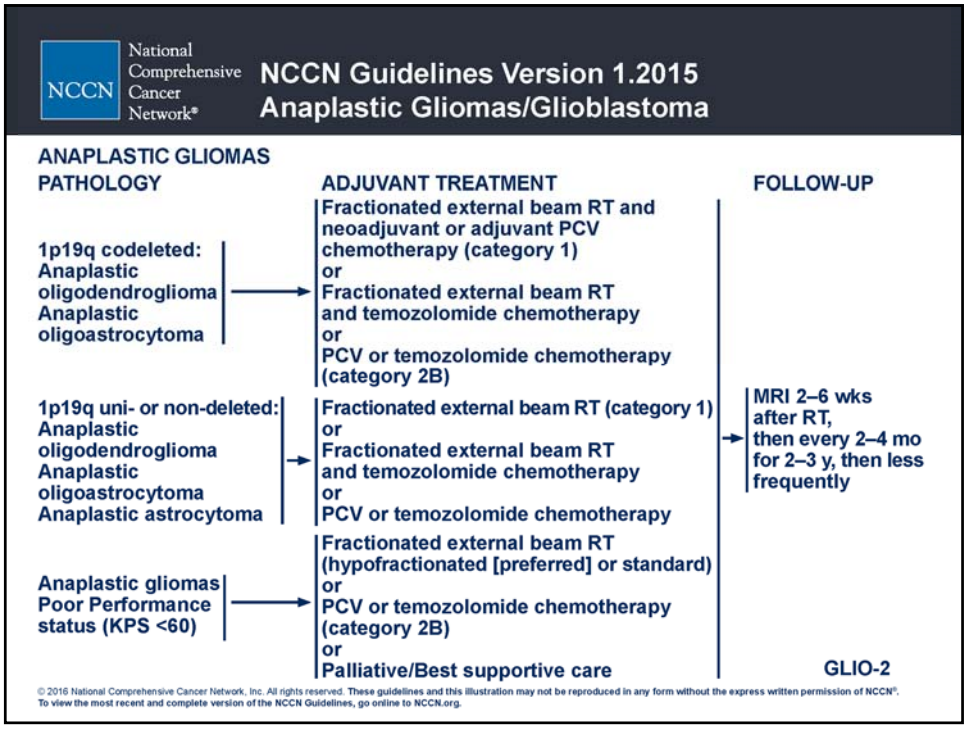


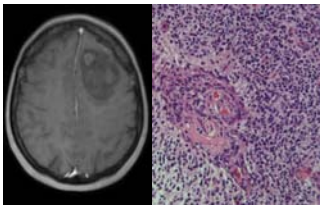
Key Points and Implications for Patient Care

- 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

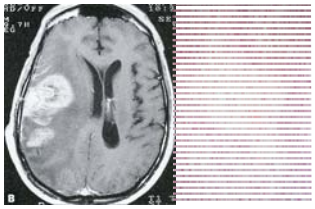
Anaplastic Astrocytoma

- 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



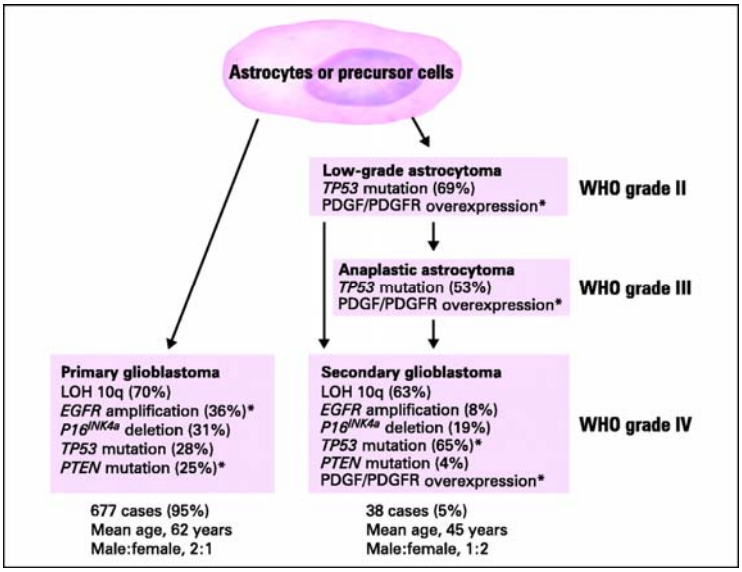
Glioblastoma Multiforme

- 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



Levin VA, et al. Neoplasms of the central nervous system. In: Cancer Principles and Practice of Oncology, 5th ed. 1997:2022-2082.

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



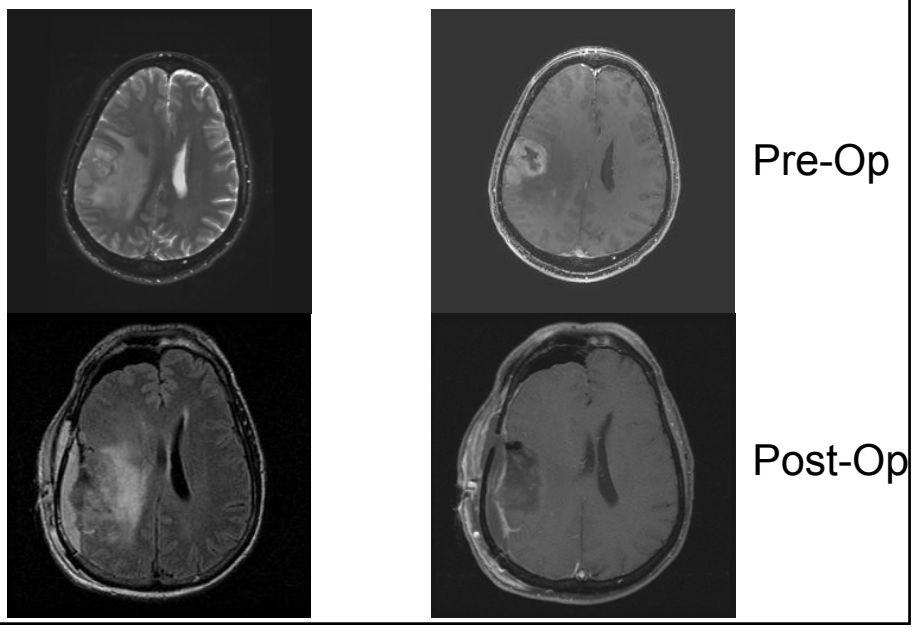
- Indicates genetic alterations that are significantly different in the frequency between primary and secondary glioblastoma multiform tumors

Reardon DA, et al. J Clin Oncol 2006;24:1253-1265.

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

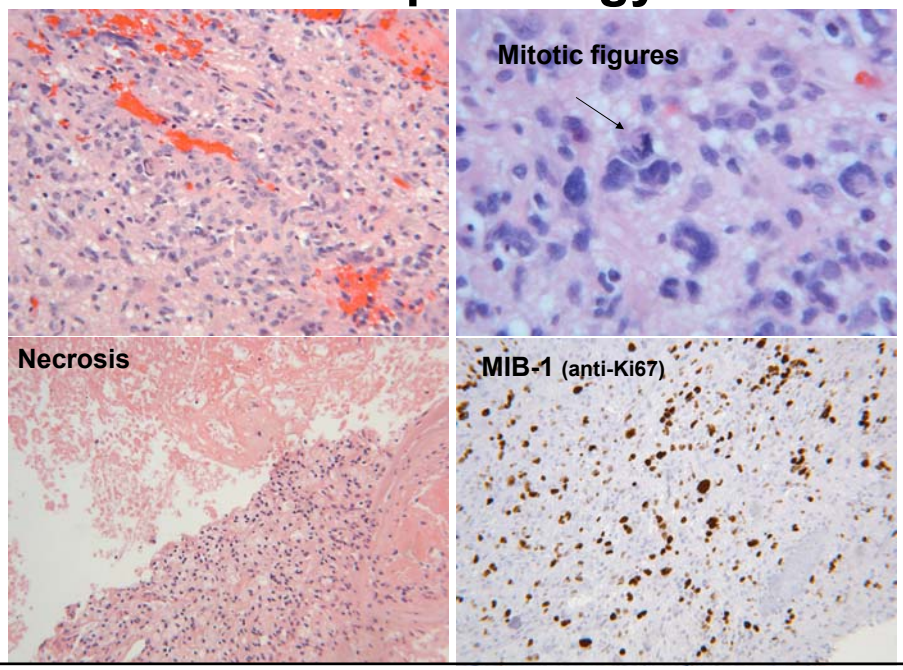
Imaging



Pre-Op

Post-Op

Neuropathology



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.

Audience Polling Results

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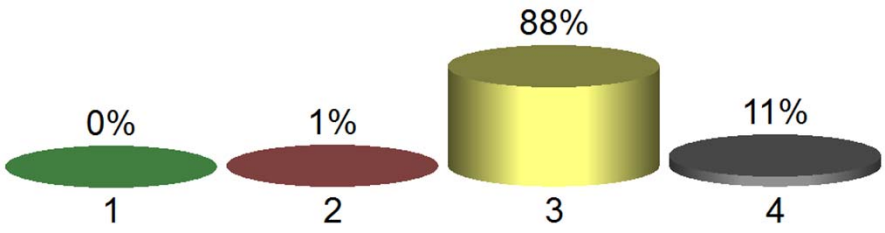


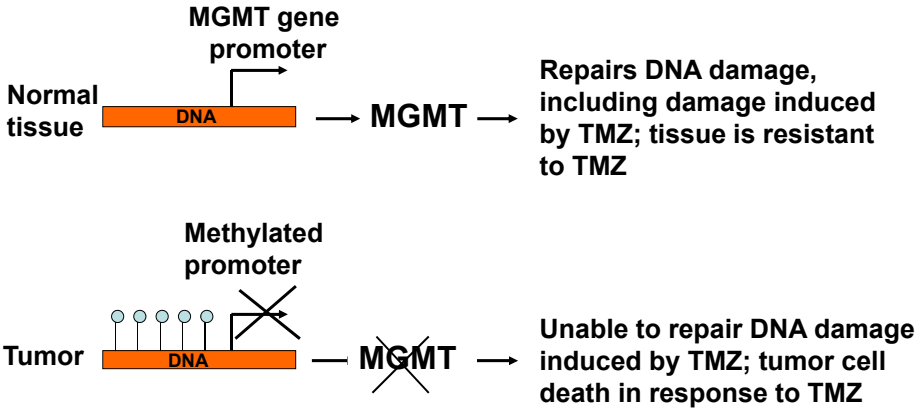
EORTC 26981-22981: Phase III Randomized Trial in Newly-Diagnosed Resected Glioblastoma

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

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

Stupp R, et al. N Engl J Med 2005;352:987-996.

Inactivation of the Methylguanine Methyl-transferase (*MGMT)* by Promoter Methylation

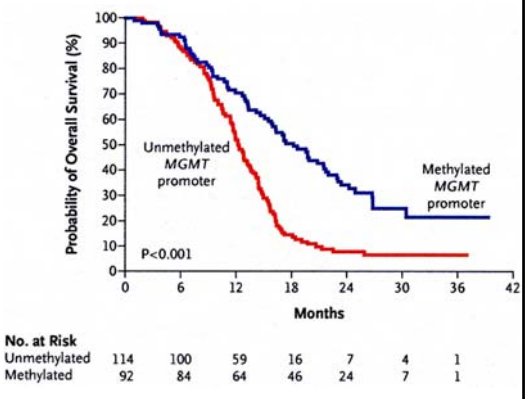


TMZ, temozolomide.

EORTC 26981-22981: *MGMT* Promoter Status and Survival

Table 1. Effect of *MGMT* Promoter Methylation Status on Survival, According to Random Treatment Assignment.*

Promoter Status and Outcome	Radiotherapy (N=100)	Temozolomide plus Radiotherapy (N=106)
Methylated *MGMT* promoter		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.0)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00	0.48 (0.31–0.75)
Overall survival		
Median duration (mo)	15.3 (13.0–20.9)	21.7 (17.4–30.4)
Rate at 2 yr (%)	22.7 (10.3–35.1)	46.0 (31.2–60.8)
Hazard ratio for death	1.00	0.51 (0.31–0.84)
Unmethylated *MGMT* promoter		
No. of patients	54	60
Progression-free survival		
Median duration (mo)	4.4 (3.1–6.0)	5.3 (5.0–7.6)
Rate at 6 mo (%)	35.2 (22.5–47.9)	40.0 (27.6–52.4)
Hazard ratio for death	1.00	0.62 (0.42–0.92)
Overall survival		
Median duration (mo)	11.8 (9.7–14.1)	12.7 (11.6–14.4)
Rate at 2 yr (%)	<2†	13.8 (4.8–22.7)
Hazard ratio for death	1.00	0.69 (0.47–1.02)



Hegi ME, et al. N Engl J Med 2005;352:997-1003.

Clinical Trials

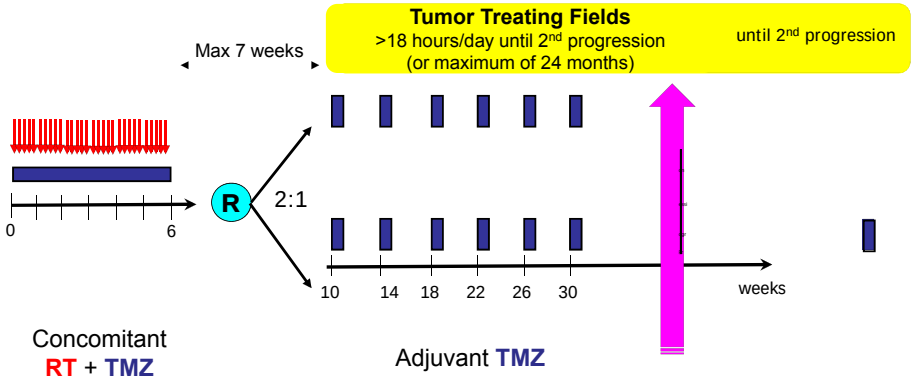
- **Alliance A071102 (NCT02152982):** A Phase II/III Randomized Trial of Veliparib or Placebo in Combination With Adjuvant Temozolomide in Newly Diagnosed Glioblastoma With MGMT Promoter Hypermethylation
- **CheckMate 498 (NCT02617589):** A Randomized Phase III Open Label Study of Nivolumab vs. Temozolomide 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

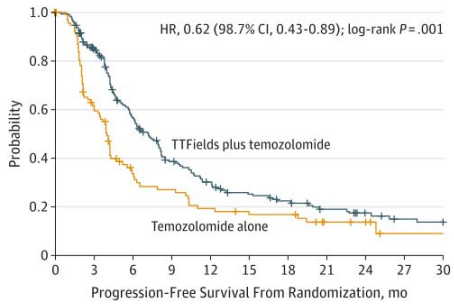


Stratification:
- **Extent resection (complete versus partial versus biopsy)**
- **MGMT methylation status**

TMZ, temozolomide
Stupp R, et al. JAMA 2015;314:2535-2543.

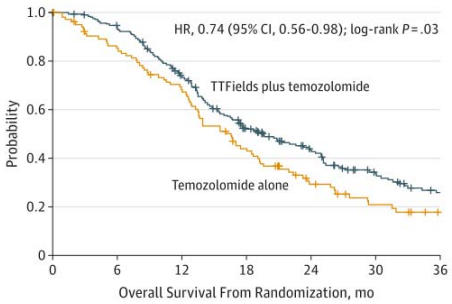
EF14 Trial Results

Progression-free Survival
(Primary endpoint, ITT population)



	TTF + TMZ	TMZ
Median	7.1 months	4.0 months
95% CI	5.9-8.2 months	3.3-5.2 months
Log Rank	P = .001	
Hazard Ratio	0.62	

Overall Survival
(Secondary endpoint, ITT population)

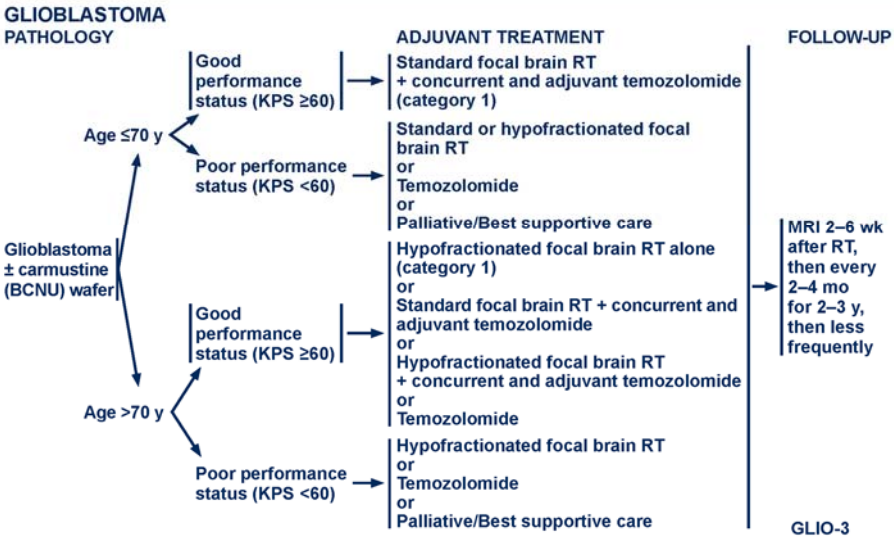


	TTF + TMZ	TMZ
Median	19.6 months	16.6 months
95% CI	16.6-24.4 months	13.6-19.2 months
Log Rank	P=.03	
Hazard Ratio	0.74	

TMZ, temozolomide; TTF, tumor treating fields.
Stupp R, et al. JAMA 2015;314:2535-2543.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
Anaplastic Gliomas/Glioblastoma



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