

**The Role of Chemotherapy
 in the Treatment of Brain Tumors**

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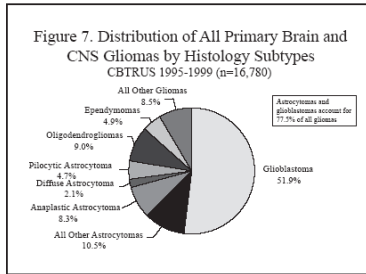
The Role of Chemotherapy in the Treatment of Brain Tumors

- Objectives:
 - 1) Describe what is a “Low Grade Glioma.”
 - 2) Describe the epidemiology of Low Grade Glioma.
 - 3) Describe the common presentation of Low Grade Glioma.
 - 4) Describe the treatment options for patients with Low Grade Glioma.

The Role of Chemotherapy in the Treatment of Brain Tumors

Brain Tumors

- Intra-cranial Tumor
 - Primary Brain Tumors
 - Glial Tumor (Gliomas)**
 - Neuronal Tumors
 - Other Tissues of the Brain
- Extra-axial Tumors
 - Meningioma
 - Chordoma
- Metastatic Brain Tumors
 - Lung
 - Breast
 - Renal
 - Melanoma

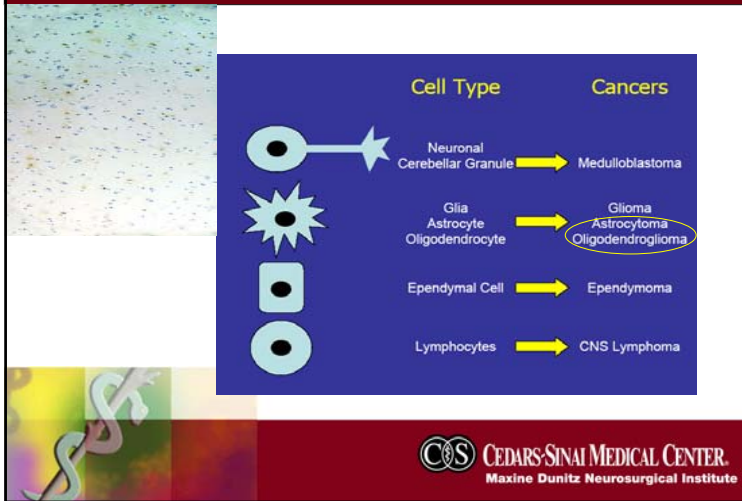


From CBTRUS 2002
 The number of metastatic brain tumor is significantly greater than primary brain tumors.

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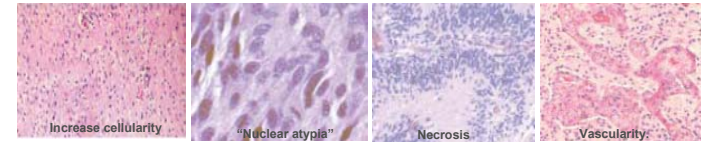
- Simplified classification of brain tumours**
- Tumours of neuroepithelial tissue**
 - Astrocytic tumours—piloicytic astrocytoma (grade I); diffuse astrocytoma (grade II); anaplastic astrocytoma (grade III); glioblastoma (grade IV)
 - Oligodendroglial tumours—oligodendroglioma (grade II); anaplastic oligodendroglioma (grade III)
 - Mixed gliomas—oligoastrocytoma (grade II); anaplastic oligoastrocytoma (grade III)
 - Ependymal tumours**
 - Choroid plexus tumours**
 - Pineal parenchymal tumours**
 - Embryonal tumours**
 - Medulloblastoma
 - Primitive neuroectodermal tumours
 - Meningeal tumours**
 - Meningioma
 - Other meningeal tumours
 - Primary CNS lymphoma**
 - Germ-cell tumours**
 - Tumours of the sellar region**

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- Gliomas
- Various grading systems: St Anne/Mayo, Ringertz, Kernohan, WHO.
- WHO Grading System:
Based on:



Children:
Grade I- "polycystic astrocytoma."

Adults:
Grade II ← Low Grade/Benign Glioma/Diffuse Astrocytoma
Grade III
Grade IV → Malignant Glioma



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The World Health Organization Grading System of Gliomas:

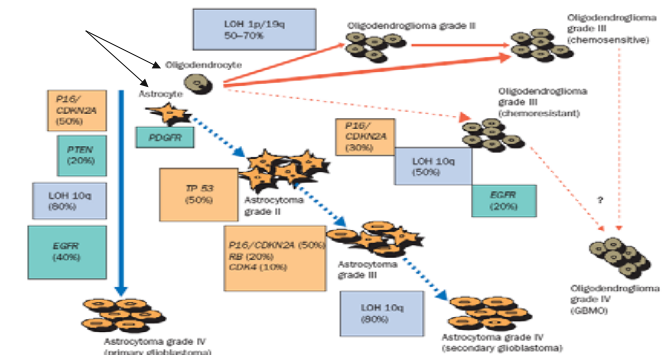
WHO Grade	WHO Designation	Histologic Criteria
II	Diffuse astrocytoma Low Grade Glioma	One criterion usually nuclear atypia.
III	Anaplastic astrocytoma	Two criteria, usually nuclear atypia and mitotic activity.
IV	Glioblastoma Multiforme	Three criteria: nuclear atypia, mitoses, endothelial proliferation and/or necrosis

Adapted from Kleihues & Canene In Press 2000



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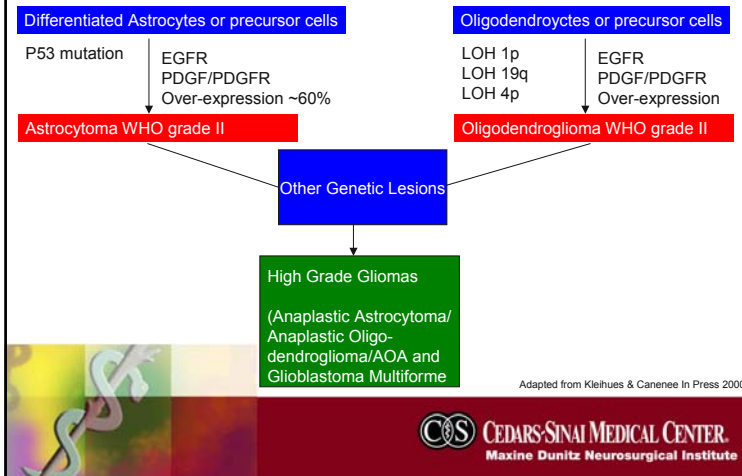
There are important cumulative genetic alterations that lead to malignancy



From Behnd et al 2003



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- Low Grade Gliomas are divided into:
 - Those from Astrocytes (Well differentiated Astrocytoma)
 - Those from Oligodendrocytes (Well differentiated Oligodendroglioma)
 - Or a combination of Astrocytes and Oligodendrocytes (Mixed Low Grade Glioma).

The well differentiated astrocytoma and well differentiated oligodendroglioma have different prognoses.



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Well differentiated Astrocytoma

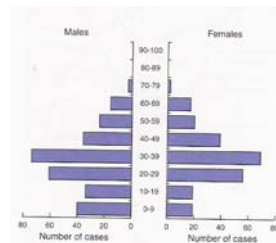
Incidence:

10-15% of all astrocytic brain tumors
1.4 cases per million / year
1500 new cases / year in North America

Age and Sex Distribution:

Peak incidence 20-40 years of age (60 % of all cases)

<20 years---10%
>45 years---30%



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Well differentiated Astrocytoma

Location

- Cortex
- 30% occur in the frontal or temporal cortices and most are not multi-focal.
- Next most common location is the brain stem and spinal cord
- Uncommon in the cerebellum



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Well differentiated Astrocytoma

- Clinical Symptoms:
 - Seizure
 - Language abnormalities
 - Sensations
 - Headache
 - Vision changes
 - Motor changes (weakness)
 - Behavioral Changes/Personality changes

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Well differentiated Astrocytoma

- Predictive Factors:
 - Mean survival time 6-8 years.
 - Continued genetic instability and the accumulation genetic lesion leads to mean time to high grade recurrence of 4-5 years.
 - Tissue obtained with p53 mutation does not excluded long term survival (without added mutations including LOH 10 and/or 19q) .

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Well differentiated Oligodendroglioma

- Incidence:
 - CBTRUS: 0.3/100,000 (including AOs)
 - 4.2% of all primary tumors
 - Other studies 5-18 % of primary tumors.
- Age and Sex Distribution:
 - Mean age 42.6 years
 - 6% occur in childhood
 - M:F-1.1-2:1



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Well differentiated Oligodendroglioma

- Location:
 - 50-60% occur in the frontal cortex followed by temporal, parietal and occipital.
- Clinical Symptoms:
 - Most commonly ...seizures.
 - Headache.
 - Motor symptoms
 - Vision changes

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Well differentiated Oligodendroglioma

- Predictive Factors:
 - Clinical Factors:
 - Age
 - Location
 - Activities of daily living
 - No enhancement
 - Extent of surgical resection

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Well differentiated Oligodendroglioma

- Pathologic Factors:
 - LOH 1p19q
 - 50-80% WDO
 - LOH 1p more specific than LOH 19q (LOH 19q also found in HGG).
 - Most importantly LOH 1p19q found to be related to increase in survival and increase in response to chemotherapy (Carnicross et al 1998; Bauman et al 2000; Smith et al 2000).
 - LOH 1p associated with prolonged survival and response to Temozolomide as compared those patients that did not have 1p loss associated with there tumors (Chahlvi et al 2004).

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- Strategies for the management of Low Grade Glioma:
 - 1)Observation
 - 2)Surgery
 - 3)Radiation Therapy
 - 4)Chemotherapy

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Observation:

- If the patient's clinical manifestation of LGG is only seizure and seizures are controlled by medication this may be a reasonable option.
- With the advent of very sensitive methods to evaluate the brain and its contents using MRI* some clinicians will follow the patient with serial imaging (every 3 months x 1 year, every 6 months x 1year then every year.

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Surgery:

Stereotactic Biopsy:

When the brain tumor is located in "eloquent cortex" or in a surgically inaccessible location (thalamus, brain stem).

Sampling Error

There are only retrospective reviews comparing biopsy vs. resection and the impact on overall survival.



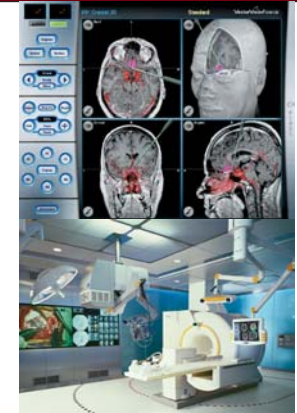
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Surgery:

Resection:

Technology to assist with tumor resection:

- Imaging guided navigation systems
- Cortical Mapping
- Functional Imaging



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Radiation Therapy:

Controversies:

Retrospective Data

Does "Early" Radiation increases survival?-

- Yes (Shaw et al 1994; Shibamoto et al 1993)
- No (Janny et al 1994; Pipmeier JM 1987, Philippon JH et al 1993)

Does radiation therapy adversely effect quality of life?

- Yes (DeAngelis et 2000) N=63. No difference in overall survival in patients that received either RT or chemotherapy. Chemotherapy was associated with early toxicity though late toxicity was seen in 1/3 of patient that received RT (neuro-toxicity/cognitive deficits). No added outcome benefit though decrease in neurocognitive functioning.

- No (Taylor et al 1998) N=701 HGG using MMSE. No reported change in MMSE at 6,12,18,24 months.

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Radiation Therapy:

EORTC trial 22844:

- 1) Is there a dose response relationship for the treatment of LGG with RT?
EORTC trial 22844: N-379 after biopsy or surgery received either 45 Gy over 5 weeks vs 59.4 Gy over 6.6 weeks. Patients were equally divided between dose levels. PFS=47%, 50%, No difference in PFS.
- 2) Is quality of life adversely affected by higher radiation dosing?
EORTC trial 22844: see above. QoL questionnaire. Statistically significant decrease in QoL for patients that received higher dose though no difference in OS.

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Chemotherapy for Low Grade Gliomas:

Few regimens have been evaluated in small population including:

Children

- Carboplatin
- Ifosfamide/Etoposide/Carboplatin
- Carboplatin/Vincristine

Adults

- Procarbazine/Carmustine/Vincristine (PCV)
- Temozolomide



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Chemotherapy for Low Grade Gliomas: PCV for Low Grade Glioma

1) Therapy has largely focused on the treatment of low grade oligodendrogliomas with LOH of 1p19q based on the response of AO with LOH1p19q (Carincross 1998).

Neoadjuvant (Before Radiation Therapy)

→Mason et al 1998. N=8 PCV WDO. Sustained responses were seen, 35 months (22-45months). Significant myelo-suppression.

→NCCTG (2003) N=28 PCV up to 6 cycles then RT. 29-52% response rate (n/o vs. radiologist) significant toxicity 75% grade 3-4 hematologic toxicity. No relationship btw 1p19q status and response.

→Van den Bent et al () N=12 (7 newly diagnosed /5 recurrent) WDO. Large lesions, unresectable and problematic to radiate. Newly diagnosed-1/7 response and Recurrent-1/5 responses.

Adjuvant (After Radiation Therapy)

→SWOG 1980 RT vs. RT then CCNU. Closed due to slow accrual.



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Chemotherapy for Low Grade Gliomas:

Temozolomide for Low Grade Glioma

2) There are currently limited numbers of prospective studies evaluating chemotherapy for adult low grade glioma and four studies have evaluated Temozolomide for the treatment of LGG only one study evaluated chemotherapy for both low grade oligodendrogliomas and astrocytomas.

Study	Patients	Pathology	RT	Chemo	Response	1_year PFS	Grade 3/4 toxicity
Quinn et al	46	A* O Mixed	15%	20%*	61%	76%	13%
Pace et al	43	A O Mixed	65%	37%	47%	39%	23%
Brada et al	30	A O Mixed	0%	0%	10%	>90%	3%
Hoang-xuan et al	60 ^f	O Mixed	0%	0%	17%	73%	8% ^g *polycystic astrocytomas ^h 1 PCV, 1 carboplatin, 1 cyclophosphamide



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Chemotherapy for Low Grade Gliomas:

The treatment of gliomas has until recently focused on chemotherapy that:

- 1) Indiscriminately damages DNA of tumor cells and of normal cells and resulting in significant toxicity (side effects).

Understanding the biology of brain tumor has led to important development in therapy for brain tumors:

- 1) Example-LOH 1p19q in low grade and high grade oligodendroglial tumor is associated with improved response to chemotherapy.
- 2) The development of small molecules inhibitors that target specific intracellular mechanisms associated with the underlying genetic or intracellular lesions found within tumors.



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Chemotherapy for Low Grade Gliomas:

Small Molecule inhibitors:

Angiogenesis

VEGF (PTK787/Endostatin/

EGF(ZD1839/Tarceva-OSI)

PDGF (STI-571)

$\alpha\beta 3$ (Celengitide)

Cell Growth

EGF

mTor (CCI-779/Rapamycin)

Histone-D Acetylase (SAHA)

Farnasyltransferase (Sch66366)

TGF- β

Raf Kinase

Apoptosis

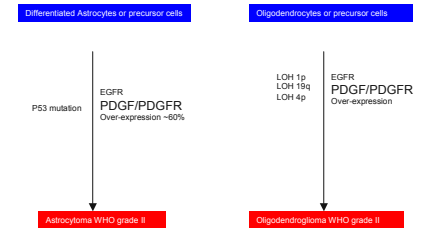
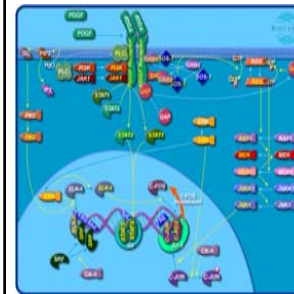
mTor

Heat Shock Proteins



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Chemotherapy for Low Grade Gliomas:



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Chemotherapy for Low Grade Gliomas:

A Phase II Study of Imatinib Mesylate for Recurrent Low Grade Glioma

OBJECTIVES:

Primary endpoint: Determine the efficacy objective response rate, 12 and 18 -month PFS of daily therapy with Imatinib mesylate in patients with progressive LGG.

Secondary endpoint: Determine the toxicities of daily therapy in patients with progressive LGG.

Histopathology

Well-differentiated oligodendroglioma

Well-differentiated astrocytoma

Mixed glioma

Polycystic Astrocytoma

Non-biopsied optic nerve or supra-sellar glioma



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More clinical Trials are need for the assessment of various biological and chemotherapies for the treatment of Low Grade Gliomas

<http://www.clinicaltrials.gov>

Biological Therapy Following Surgery and Radiation Therapy in Treating Patients With Primary or Recurrent Astrocytoma or Oligodendroglioma.

Consortium

NABTT (New Approaches to Brain Tumor Therapy)

NABTC (North American Brain Tumor Consortium)





Burt Rutan 2004 "The biggest obstacle we had to overcome was not the engineering problem, personnel problems it was getting people to believe ..."



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Thank You

Presentations may be down loaded from:
www.cedars-sinai.edu/brainumor

