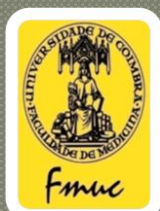




# GLIOMAS

## da epidemiologia ao tratamento



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Serviço de Neurocirurgia CHUC  
Unidade Curricular Neurocirurgia FMUC



# Tumores cerebrais

## Epidemiologia

- 1,4% de todos os tumores (ACS)
- 2,4% das mortes por tumores (ACS)
- primitivos 14/100.000/ano (CBTRUS)
- 1/2 malignos, 1/3 gliomas  
(4,5/100.000/ano – 450 gliomas/ano)

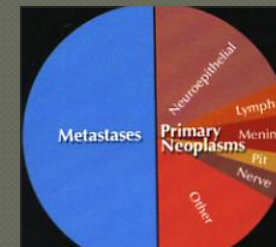
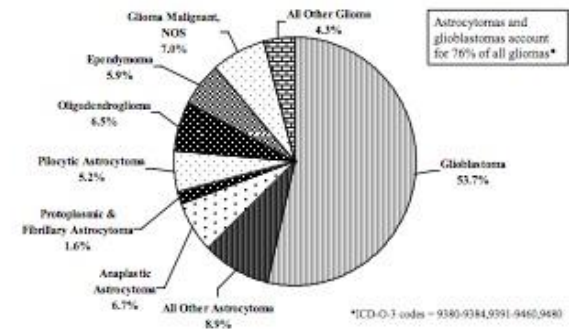
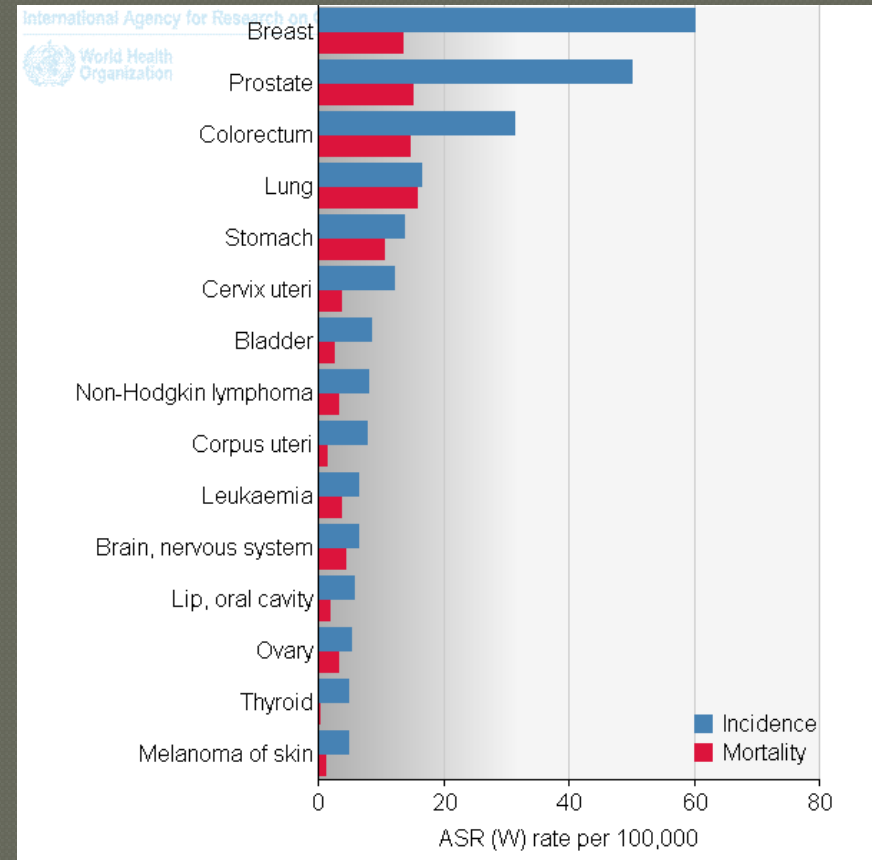
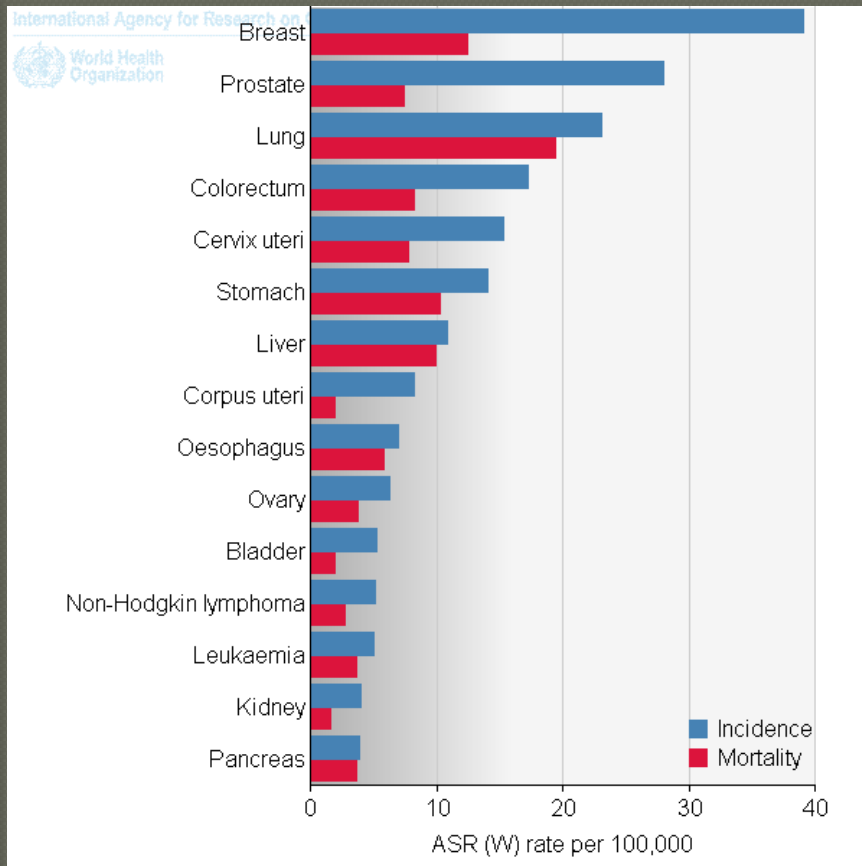


Figure 7. Distribution of All Primary Brain and CNS Gliomas\* by Histology Subtypes (N=70,528)

CBTRUS Statistical Report: NPCR and SEER Data from 2004-2007



# Tumores cerebrais

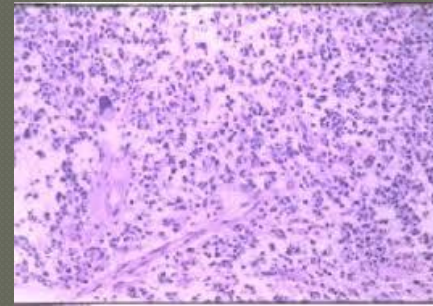


3,7/100.000/ano M  
2,6/100.000/ano F

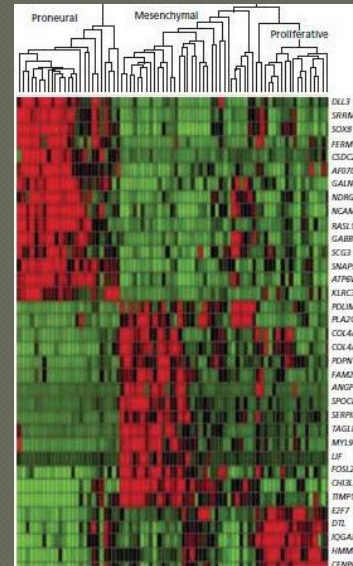
(IARC – globocan project)

# Tumores cerebrais

## Classificação OMS (2007)



## Caracterização genética

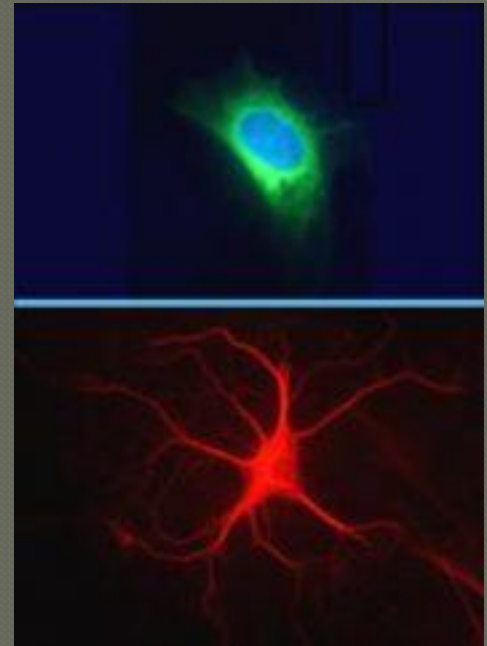


# Tumores cerebrais

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## Tumores Neuroepiteliais

- Gliomas
- Tumores embrionários
- Tumores neuronais
- Tumores dos plexos coroides
- Tumores da pineal



# Tumores cerebrais

## ● Tumores astrocitários

### Astrocitomas localizados

*Pilocítico (I)*

*Pilomixoide (I)*

*Subependimario células gigantes (I)*

*Xantoastrocitoma pleomórfico (II/III)*

### Astrocitomas difusos

*Fibrilhar (II)*

*Gemistocítico (II)*

*Protoplasmico (II)*

*Anaplásico (III)*

*Glioblastoma (IV)*

*Glioblastoma células gigantes (IV)*

*Gliosarcoma (IV)*

*Gliomatose cerebral (IV)*

## ● Tumores oligodendrogliais

Oligodendroglioma (II)

Oligodendroglioma anaplásico (III)

## ● Tumores oligoastrocitários

Oligoastrocitoma (II)

Oligoastrocitoma anaplásico (III)

## ● Tumores ependimários

Subependimoma (I)

Ependimoma mixopapilar (I)

Ependimoma (II)

*Celular*

*Papilar*

*Células claras*

*Tanicítico*

Ependimoma anaplásico (III)

# Tumores cerebrais

Authors	Potential Risk Factor	Outcome of Selected Epidemiologic Studies
Wenzsch et al. <sup>10</sup>	Alcohol	Slight to no association. <sup>10</sup>
Schiebler et al. <sup>10</sup> Wenters et al. <sup>10</sup> Benner et al. <sup>10</sup> Inskip et al. <sup>10</sup> Mustali et al. <sup>10</sup>	Allergies	An inverse association of allergic diseases with glioma. <sup>10,11,12</sup> Statistically significant inverse dose response of glioma with increasing numbers of allergies. <sup>10</sup>
Coggans et al. <sup>10</sup> Dien et al. <sup>10</sup> Espuru-Carrivage et al. <sup>10</sup> Kelsey et al. <sup>10</sup> Tizna <sup>10</sup>	Cellular telephones	No association found in current studies. <sup>10,13</sup>
Biel et al. <sup>10</sup> Lubin et al. <sup>10</sup> Wenzsch et al. <sup>10</sup>	Constitutive polymorphisms (in carcinogen-metabolizing, DNA repair, and immune function genes)	Silent polymorphisms in DNA repair genes linked to oligoastrocytoma, <sup>13</sup> glioblastoma, <sup>14</sup> and astrocytoma. <sup>15</sup> Conflicting results for associations of cytochrome p450D6 and glutathione transferase theta polymorphisms with increased risk. <sup>10,16,17</sup>
Pester-Martin & Mack <sup>10</sup>	Diet and vitamins	Mixed support for association of <i>N</i> -nitroso compounds, antioxidants, or specific nutrients with adult or childhood brain tumors. <sup>10,18</sup>
Lolo et al. <sup>10</sup> Schiebler et al. <sup>10</sup> Wenzsch et al. <sup>10</sup>	Drugs and medications	Few statistically significant or consistent findings between brain tumor development and studied drugs. <sup>10</sup>
Bondy et al. <sup>10</sup>	Epilepsy, seizures, or convulsions	Some association; causality is difficult to determine, because seizures are often a symptom of brain tumor. <sup>10,19</sup>
Inskip et al. <sup>10</sup> Gavin & Tojev <sup>10</sup> Tate <sup>10</sup>	Familial history of brain tumors	Reported relative risks range from almost 1 to 10. <sup>10</sup> Genetics or possible common exposure to environmental factors may contribute.
Lubin & Wolf <sup>10</sup> Pester-Martin & Mack <sup>10</sup> Wenzsch et al. <sup>10</sup>	Hereditary syndromes <sup>10</sup>	Compelling evidence that certain inherited genes may strongly influence the risk of primary brain tumor development. <sup>10</sup>
Bondy et al. <sup>10</sup> Bondy et al. <sup>10</sup>	Infectious agents or immunosuppression <sup>10</sup>	Some viruses cause brain tumors in experimental animals, <sup>10</sup> but except for studies of HIV-related brain lymphomas, <sup>10,20</sup> few epidemiologic studies have evaluated a potential role of viruses in human brain tumorigenesis. <sup>10</sup>
Thomas & Wakefield <sup>10</sup>	Ionizing radiation (therapeutic, <sup>10</sup> diagnostic, other)	Diagnostic radiation and nuclear material exposure may create elevated risk for some tumor types. <sup>10,21</sup> Therapeutic ionizing radiation is a strong risk factor for brain tumorigenesis. <sup>10,21</sup>
Zahn <sup>10</sup>	Lymphocyte mitogen sensitivity (to gamma radiation)	Significantly associated with a risk of glioma. <sup>10</sup>
Wenzsch et al. <sup>10</sup>	Ozonolysis and industry	Difficult to establish an association between exposure to specific occupational or industrial chemicals and human brain tumorigenesis. <sup>10</sup> Exposure to multiple chemicals and chemical interactions are two of the complicating factors.
Teppo et al. <sup>10</sup>	Personal and residential chemical exposures	Some studies have shown a link between pesticide exposure and risk of childhood brain cancers. <sup>10</sup>
Buffetta et al. <sup>10</sup> Lee et al. <sup>10</sup>	Power frequency electromagnetic field	No causal connection between EMF and risk of brain tumor has been established. <sup>10</sup> Measurement and unknown latency are complicating factors.
Raschou-Nielsen et al. <sup>10</sup>	Prior cancers	Increased risk among patients with small cell lung carcinoma and adenocarcinoma, but interpretation complicated by possibility of confounding metastatic and primary brain tumors. <sup>10</sup>
	Tobacco smoke exposure	No major contribution of maternal tobacco smoking to risk of childhood brain tumors, <sup>10</sup> small associations with paternal smoking. No important contribution of smoking filtered cigarettes to adult brain tumors. <sup>10</sup>
	Traffic-related air pollution	No association between childhood brain tumor and exposure to traffic-related air pollution. <sup>10</sup>

- Álcool
- Tabaco
- Neoplasias prévias/história familiar
- Alergias
- Campos magnéticos alta potência
- Dieta
- Radiações/Telemóveis
- Fármacos e drogas
- Síndromes hereditários
- Fatores ocupacionais e industriais
- Infecções e imunodepressão
- Poluição rodoviária

# Gliomas cerebrais

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- OMS - “possivelmente carcinogénicos”  
(Lancet Oncology 06/2011)
- “possivelmente” = não seguramente inócuos
- INTERPHONE
- “Pooled analysis”
- Estudos epidemiológicos e experimentais

# Gliomas cerebrais

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- INTERPHONE - risco menor nos utilizadores

10% top utilização

OR = 1.40

ipsilateral, lobo temporal

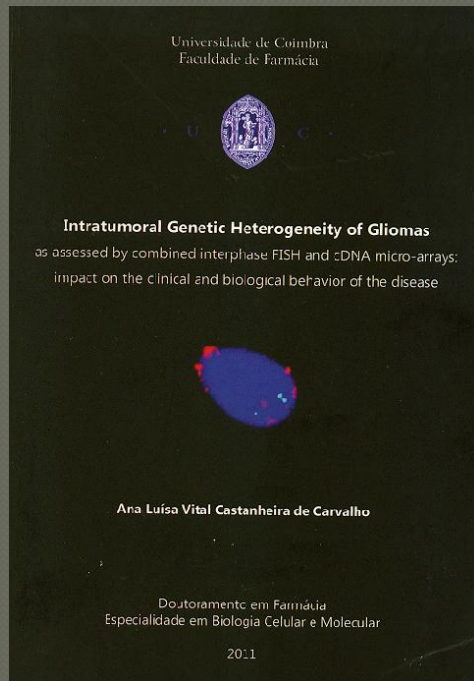
sub-grupo (TCSE)

# Gliomas cerebrais

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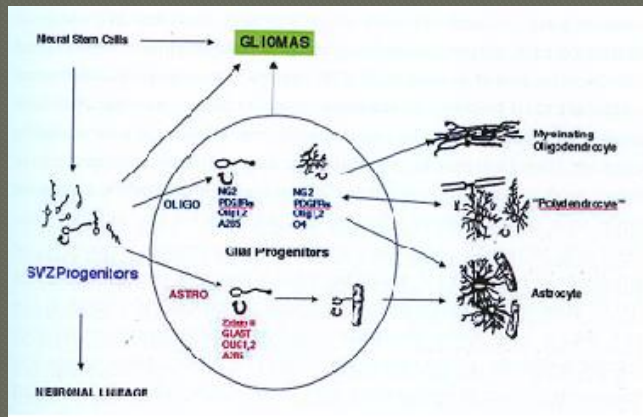
- “pooled analysis” - > 1 ano 30% superior  
3.2 x superior > 2000h  
ipsilateral
- Estudo Dinamarquês, outros
- COSMOS, MobiKids, CEFALO, MorPhEUS

# Gliomas cerebrais

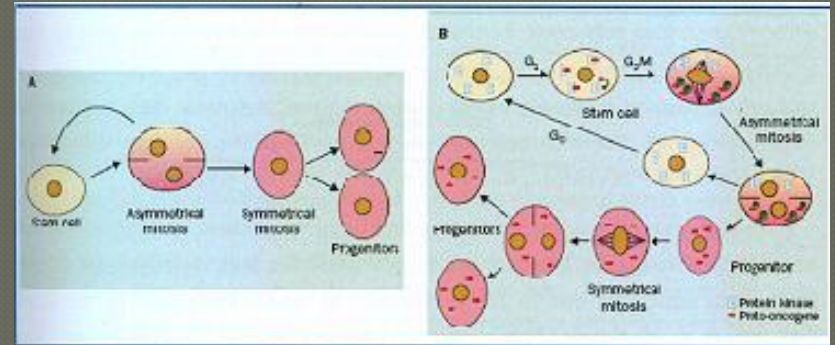


- p 53
- IDH1
- p16
- PTEN
- MDM2
- EGFR
- BCL2
- 10 e 19q
  
- MGMT
- 1p/19q

# Gliomas cerebrais

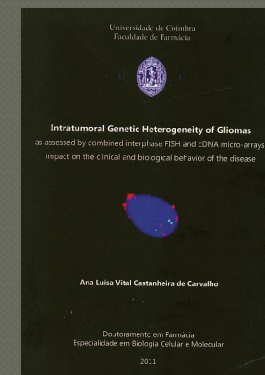
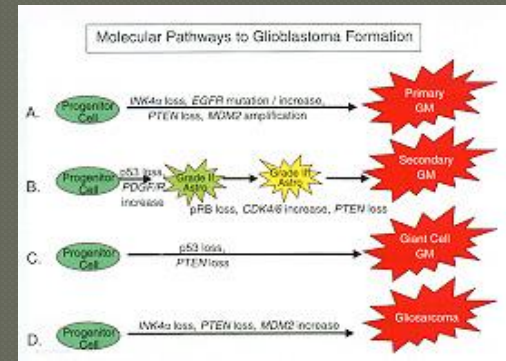
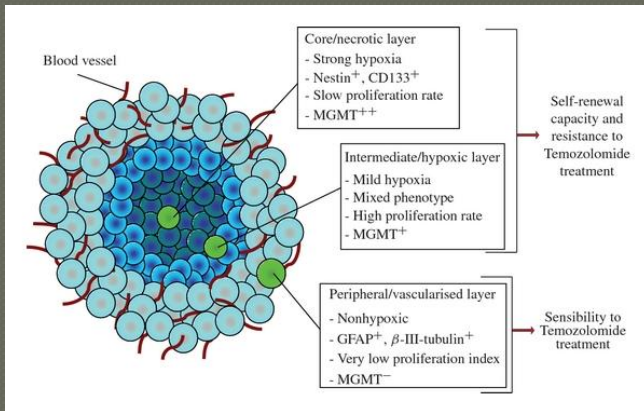
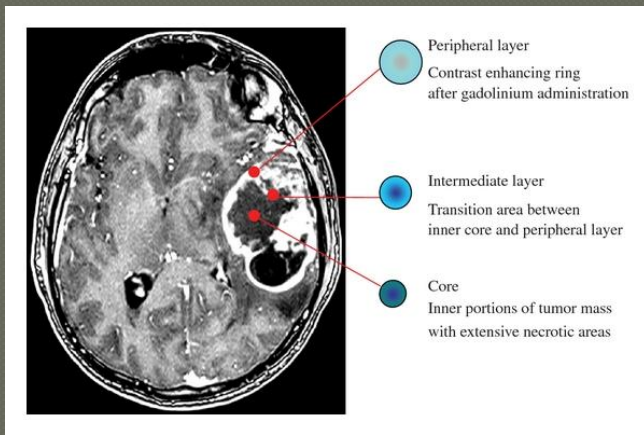


Canoll P; Goldman JE  
Acta Neuropathol; 2008



Berger F, et al  
Lancet Oncol; 2004

# Gliomas cerebrais



Persano N et al

Scientific World Journal. 2011;11:1829-41

# Gliomas cerebrais

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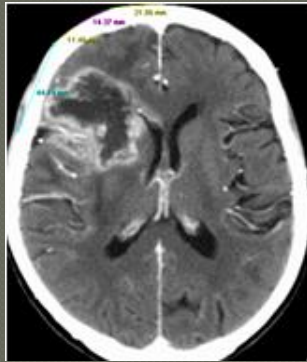
## Clínica

- Localização e volume
- Edema
- Hemorragia
- Hidrocefalia
- Assintomático – HIC
- Défice neurológico (motor, visual, fala...)
- Cefaleias
- Epilepsia

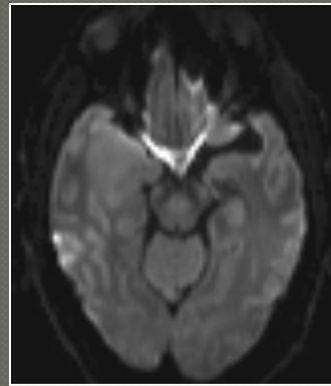
# Gliomas cerebrais

## Imagiologia

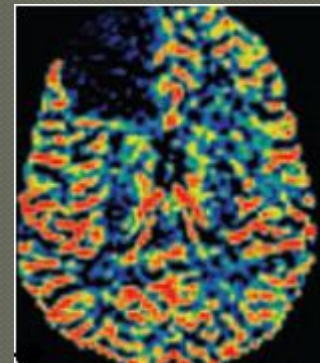
● TC



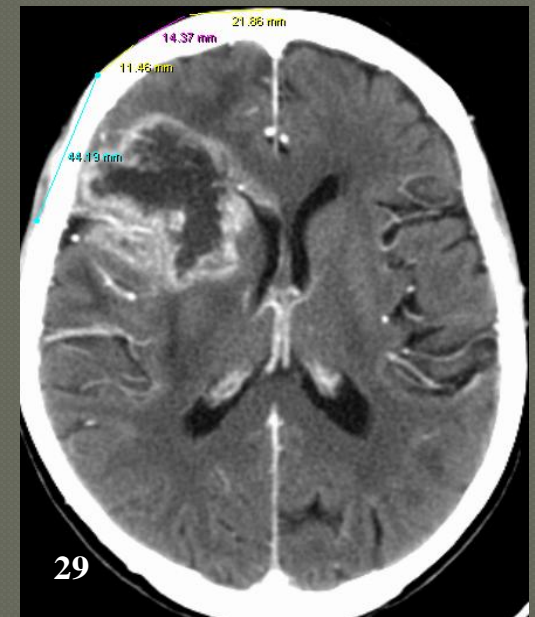
● RM



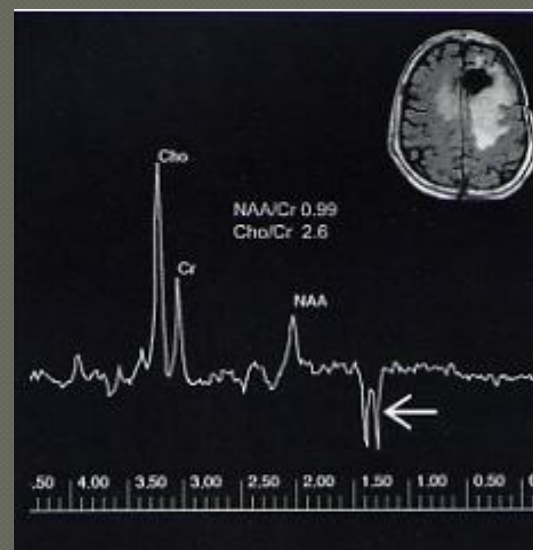
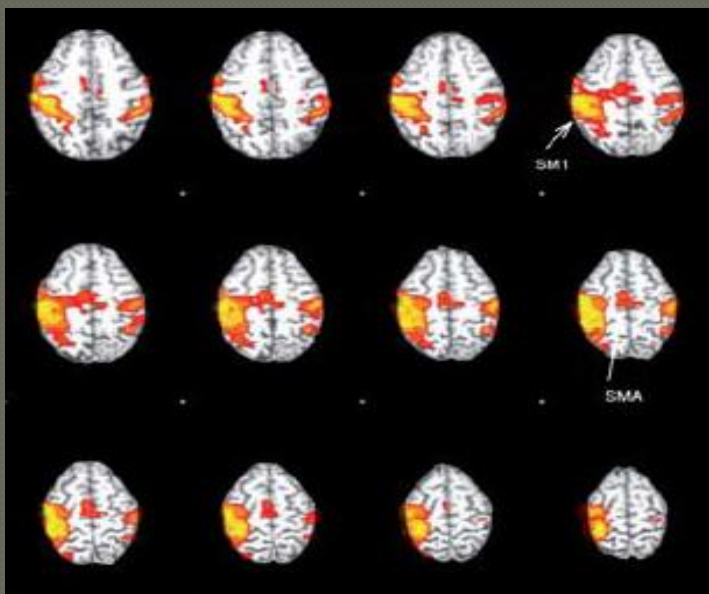
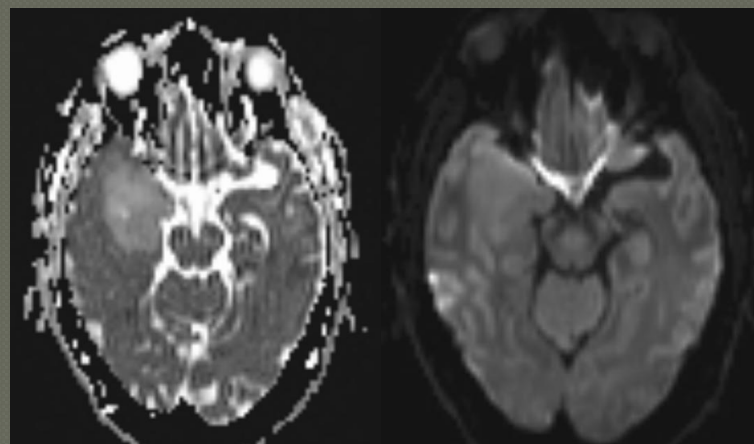
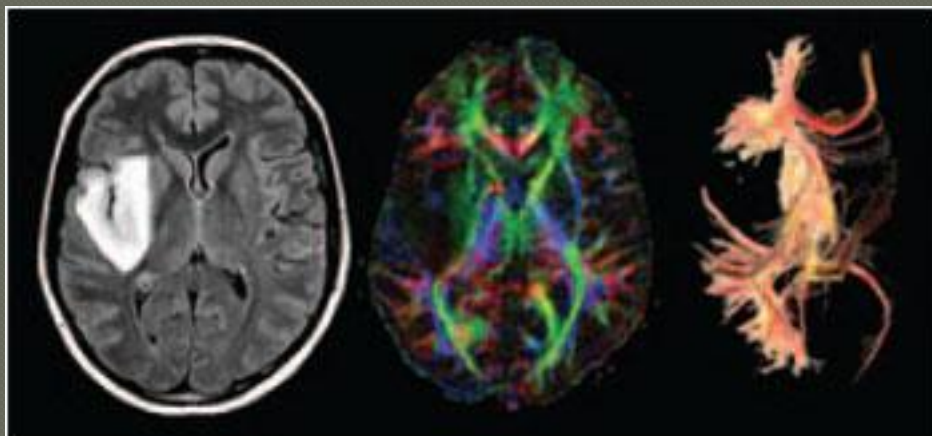
● PET



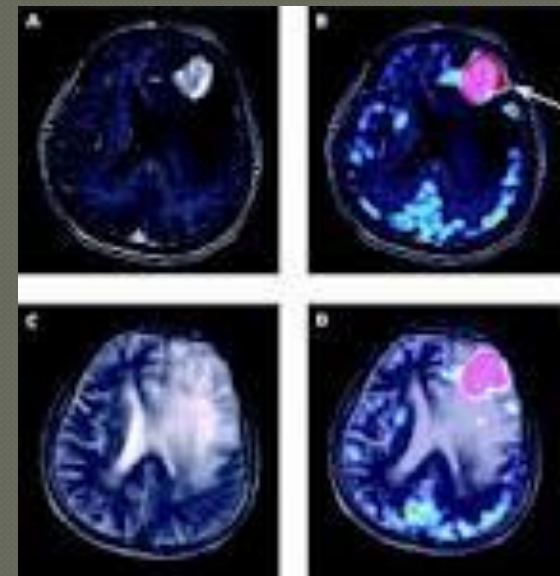
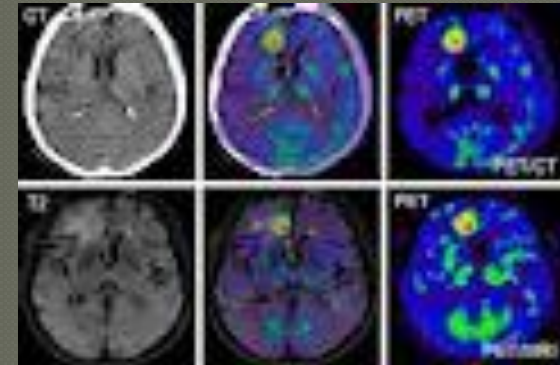
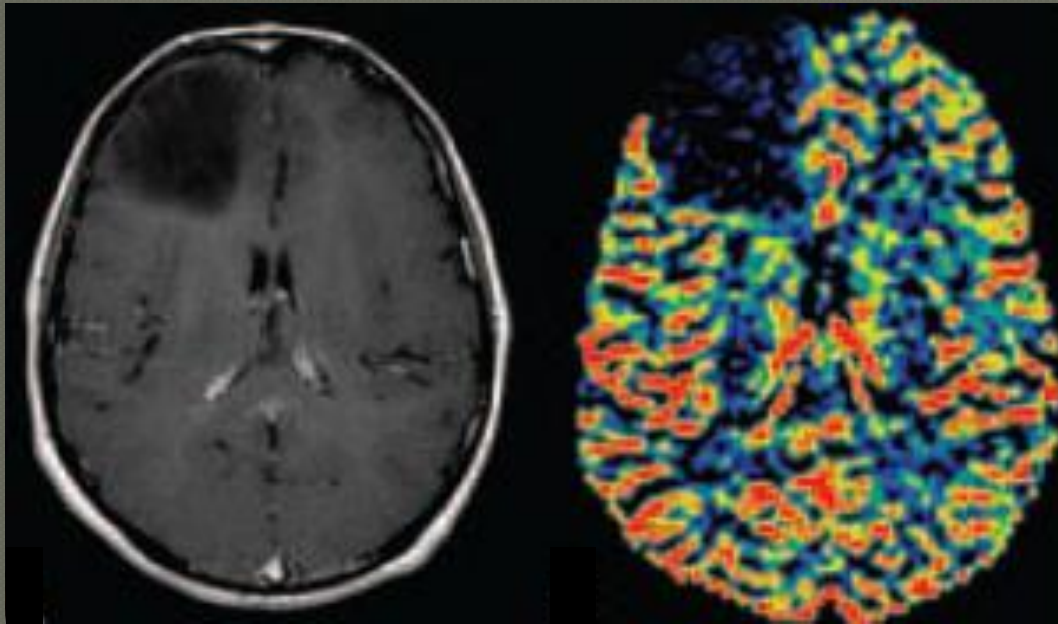
# Gliomas cerebrais



# Gliomas cerebrais



# Gliomas cerebrais



# Gliomas cerebrais

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## Tratamento

- **Cirurgia** “radical” vs “máxima segura”
- **Quimioterapia**
- **Radioterapia**
- **Outros**

# Gliomas cerebrais

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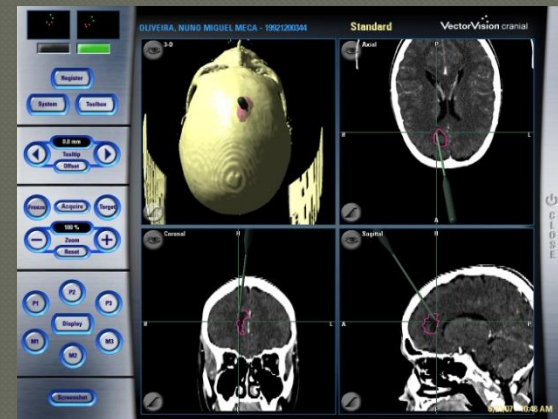
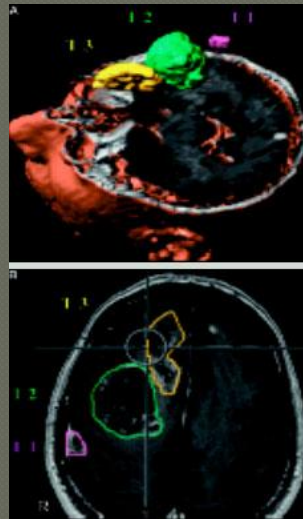
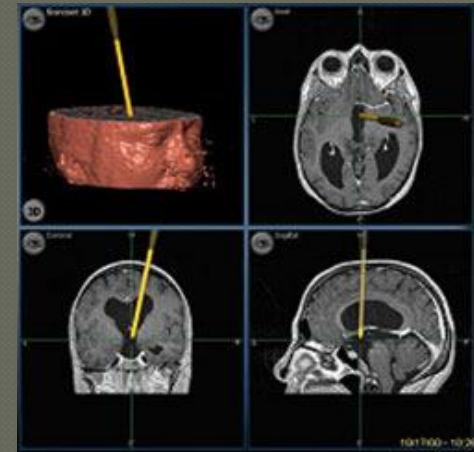
## Cirurgia

- Estereotaxia, neuronavegação
- Mapeamento cerebral
- Estimulação cortical
- Fluorescência
- TC e RM intraoperatória

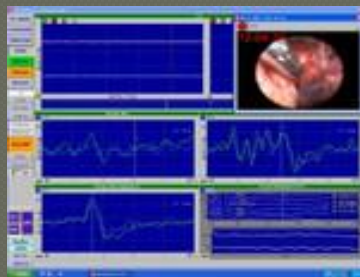
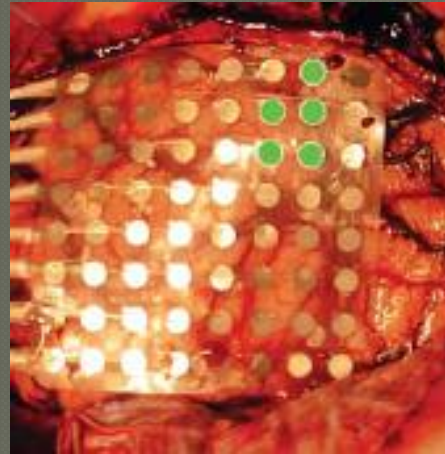
# Gliomas cerebrais



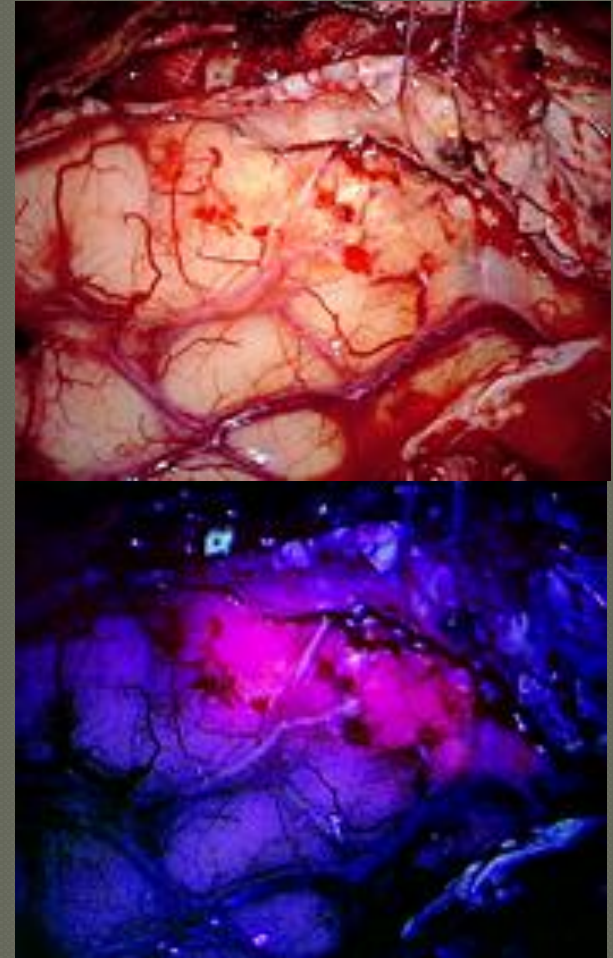
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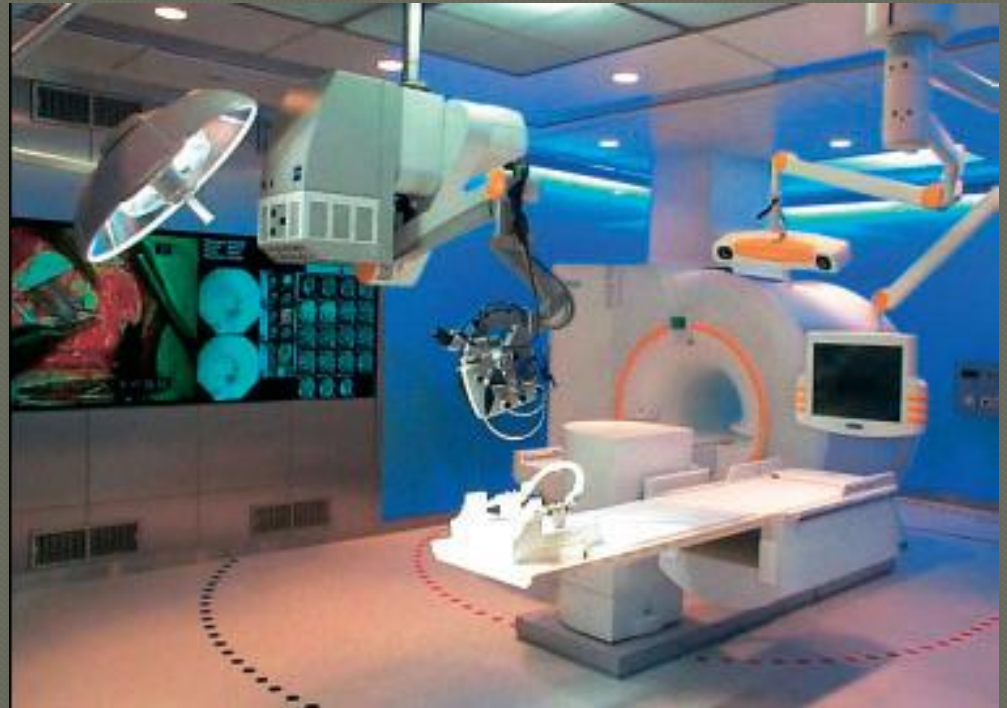
# Gliomas cerebrais



# Gliomas cerebrais



# Gliomas cerebrais



# Gliomas cerebrais

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## Tratamento

- ◉ Baixo grau - cirurgia  
radioterapia  
quimioterapia
  
- ◉ Alto grau - cirurgia  
radioterapia  
quimioterapia  
outros

# Gliomas cerebrais

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## Tratamento

- ◉ Baixo grau - **cirurgia**  
**radioterapia**  
**quimioterapia**
- ◉ EORTC + MCR ( van den Bent MJ et al. Lancet 336, 985-990; 2005)

RxT a seguir cirurgia vs após progressão do tumor

maior intervalo para a progressão (5,3 vs 3,4 anos  $p < 0,0001$ )  
sobrevida média não diferente (7,4 versus 7,2 anos)

# Gliomas cerebrais

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## Tratamento

- Baixo grau - **cirurgia**  
**radioterapia**  
quimioterapia
  
- Idade (<40 anos vs  $\geq$  40 anos)  
Dimensão (< 6 cm ou  $\geq$  6 cm)       $\leq 2 = > 7$  anos  
Linha média       $\geq 3 = \downarrow$   
Tipo histológico (oligo/astro)  
Presença ou ausência déficit

# Gliomas cerebrais

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## Tratamento

- Baixo grau - cirurgia  
radioterapia  
**quimioterapia**
- PCV; temozolamida
- Oligo (1p/19q)

# Gliomas cerebrais

---

## Tratamento

- Alto grau - cirurgia  
radioterapia  
quimioterapia  
outros

# Gliomas cerebrais

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## Radioterapia

- ◉ Holocraniana
- ◉ 3DCRT
- ◉ IMRT
- ◉ Baixo grau
- ◉ Alto grau

# Gliomas cerebrais

---

## Radioterapia

- ◉ Radiocirurgia
- ◉ Radioterapia fraccionada estereotáxica
- ◉ Braquiterapia
- ◉ Partículas - prótons e iões carbono

# Gliomas cerebrais

---

## Quimioterapia

- Carmustina (sistémica, local) ou PCV
- Stupp R, et al  
“Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma”

*N Engl J Med* 2005 Mar 10;352(10):987-96

# Gliomas cerebrais

## BACKGROUND:

Glioblastoma, the most common primary brain tumor in adults, is usually rapidly fatal. The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by adjuvant radiotherapy. In this trial we compared radiotherapy alone with **radiotherapy plus temozolomide, given concomitantly** with and after radiotherapy, in terms of efficacy and safety

## METHODS:

Patients with newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive **radiotherapy alone** (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or **radiotherapy plus continuous daily temozolomide** (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). The primary end point was overall survival.

## RESULTS:

A total of 573 patients from 85 centers underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, **the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone.** The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95 percent confidence interval, 0.52 to 0.75;  $P < 0.001$  by the log-rank test). **The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone.** Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 hematologic toxic effects in 7 percent of patients.

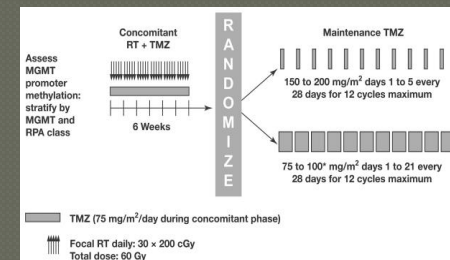
## CONCLUSIONS:

The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a **clinically meaningful and statistically significant survival benefit** with minimal additional toxicity.

# Gliomas cerebrais

## Quimioterapia

- Metilação gene promotor/depleção actividade MGMT  
(mOS 21,7 meses vs 12,7 e OS 2 anos 46 vs 13,8%)
- Múltiplos regimes terapêuticos/exposição prolongada
- RTOG 2011 - dose “convencional” vs “intensiva”  
(RTOG 0525 Phase III Trial )



# Gliomas cerebrais

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## Terapêutica dirigida

- EGFR TKI (gefitinib, erlotinib...)
- VEGF (bevacizumab, sunitinib, cilengitide...)
- Outros (irinotecan, talampanel, bortezomid...)

# Gliomas cerebrais

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## Terapêutica dirigida

- Terapêutica génica (genes citotóxicos, toxinas, oncogenes supressores...)
- Terapêutica autoimune (modulação citocinas, vacinas células dendríticas...)

# Gliomas cerebrais

## Factores prognóstico

- Histologia
- Grau de remoção
- Localização
- Idade
- Karnofsky

Table 21-16 Outcome groups using RPA for GBM

Group	Characteristics	Median survival (wks)	Estimated 2-year survival
1: low risk	<ul style="list-style-type: none"><li>• age <math>\leq</math> 40 years</li><li>• frontal tumor</li></ul>	132	65%
2: low-moderate risk	<ul style="list-style-type: none"><li>• age <math>\leq</math> 40 years</li><li>• tumor outside frontal lobe</li></ul>	71	35%
3: moderate-high risk	<ul style="list-style-type: none"><li>• 40 &lt; age &lt; 65</li><li>• KPS &gt; 70</li><li>• STR or GTR</li></ul>	63	17%
4: high risk	<ul style="list-style-type: none"><li>• age <math>\geq</math> 65 years</li><li>• or 40 &lt; age &lt; 65 AND KPS &lt; 80</li><li>• or 40 &lt; age &lt; 65 AND KPS <math>\geq</math> 80 AND biopsy only</li></ul>	37	4%

# Gliomas cerebrais

## Factores prognóstico

- Histologia - grau I            8-10 anos
- grau II                7-8 anos
- grau III              2-3 anos
- grau IV              ±1 ano

- Análise molecular
- Novas terapêuticas

TABLE 19: ONE-, TWO-, FIVE-, AND TEN-YEAR OBSERVED AND RELATIVE SURVIVAL RATES\* FOR SELECTED MALIGNANT BRAIN AND CENTRAL NERVOUS SYSTEM TUMORS, SEER 1973-1999

HISTOLOGY	ICDO CODE(S)	NO. OF CASES	1-YEAR		2-YEAR		5-YEAR		10-YEAR	
			Obs.	Rel.	Obs.	Rel.	Obs.	Rel.	Obs.	Rel.
Pilocytic astrocytoma	9421, 9422	895	94.7	94.9	92.0	93.3	83.9	89.7	85.6	87.1
Diffuse astrocytoma	9410, 9420	659	72.7	73.4	69.3	61.4	44.6	46.9	34.1	38.1
Anaplastic astrocytoma	9401, 9411	1,998	59.7	60.4	43.3	44.4	28.0	30.0	19.4	22.7
Astrocytoma, NOS	9400	6,964	58.2	59.0	45.0	46.4	33.6	36.3	25.1	29.9
Glioblastoma	9440-9442, 9481	13,733	28.1	28.8	8.2	8.6	2.9	3.3	1.7	2.3
Oligodendroglioma	9450	1,524	87.9	88.5	80.1	81.3	65.7	68.2	46.8	51.1
Anaplastic oligodendroglioma	9451, 9460	256	75.0	75.8	56.8	58.1	38.1	40.5	24.5	27.7
Ependymoma/anaplastic ependymoma	9301-9303	1,038	85.0	86.3	78.6	79.5	65.9	67.9	55.3	59.0
Mixed glioma	9382	664	83.6	84.1	71.9	72.8	54.4	56.3	30.0	42.3
Glioma malignant, NOS	9380	2,346	46.6	47.7	33.9	35.5	25.3	28.5	19.3	24.7
Neuroepithelial	9381, 9423, 9430, 9443	235	59.5	60.2	47.3	48.5	37.0	39.4	28.5	32.7
Malignant neuronal/glia, neuronal and mixed	8680-8682, 8690, 8693, 9490-9491, 9500, 9505, 9506, 9522-9523	154	77.1	77.4	63.6	64.0	51.3	52.1	46.3	47.5
Embryonal/primitive/medulloblastoma	8663, 9263-9364, 9470-9473, 9501-9503	1,269	79.8	80.0	70.2	70.4	53.6	54.0	45.2	45.9
<b>TOTAL: ALL BRAIN AND CNS*</b>	<b>8880-9989</b>	<b>33,896</b>	<b>50.0</b>	<b>50.9</b>	<b>35.0</b>	<b>36.4</b>	<b>25.6</b>	<b>28.2</b>	<b>19.5</b>	<b>24.2</b>

\*Data are an estimate of the percentage of patients alive at one, two, five and ten years, respectively.  
 \*Excludes histiocytosis not listed in this table, brain lymphomas, olfactory tumors of the nasal cavity, and malignant tumors of the pituitary and pineal glands are excluded.  
 Abbreviation used: SEER, Surveillance, Epidemiology, and End Results.