Brain Tumors – TREATMENT

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Treatment planning demands tissue diagnosis! see p. Onc1 >>

Final goal of therapy - CYTORESECTION - decrease of total tumor mass to size that immune system might suppress and eventually kill (for gliomas it is 0.0001 g, or 1 × 10^-4 cells).

For NEUROEPITHELIAL TUMORS, likelihood of care is small and risks to brain are large; to improve therapeutic ratio, modularity treatment is rule:

1) Surgery - usually leaves residual tumor burden of 1-5 x10^6 cells;
   a) surgery is only form of therapy in which tumor cells are not only killed but actually removed (body's capacity to remove debris from brain is less than that for other organs - removal of dead tumor tissue is valuable adjunct).
   b) if tumor bulk is reduced, quiescent cells enter active growth phase, making them more susceptible to radiation / chemotherapy!
2) Radiotherapy might kill two additional logs of cells, reducing tumor to 1 x 10^5 cells;
3) Chemotherapy must then kill two additional logs to reduce burden to desired 1 x 10^4 cells.

Present-day multimodality treatment can treat infiltrative brain tumors but can rarely cure them.

Any treatment modality requires measure of response to treatment - contrast-enhanced MRI (or less desirably, CT),
   a) tumor growth (deterioration)
   b) tumor regression (response).

SYMPTOMATIC TREATMENT

VASOGENCE EDema

Raised ICP accompanies majority of brain tumors - start Dexamethasone in every patient promptly!!!

- small meningiomas or acoustic neoplasms usually do not require treatment to reduce ICP.
- Dexamethasone is steroid of choice (lowest mineralocorticoid activity, best CNS penetration).

Dosage - start with oral loading dose of 10-24 mg → 4-10 mg x 4/6 (or 8 x 2).
   for children - start 0.5-1.1 mg/kg → 0.25-0.5 mg/kg divided into 4 daily doses.
   - well absorbed by mouth - action is almost as rapid as when given IV (can be switched from IV to PO regimen in 1:1 ratio).
   - plasma T1/2 is 2-4 hours but biologic T1/2 is 36-54 hours (OK to dose once a day).
   - induces improvement within 48 hours (usually sooner);
   - if no benefit - neurologic symptoms are due to damage of brain tissue by tumor (i.e. not to edema);
   - consider CSF diversion procedure because various degree hydrocephalus is frequent.
   - lowest dosage that maintains patients at maximum level of comfort and function should be sought (decrease dosage until symptoms increase or become apparent → increase dosage until they subside);
   - N.B. tumor growth or treatment-induced effects may require dosage↑; decrease in steroid requirement suggests improvement.
   - antilipid agent (e.g. H3-blocker) and glycerol control (e.g. insulin on sliding scale) are required.

Low-dose versus high-dose dexamethasone in metastatic brain tumors

Vecht CJ et al. Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized controlled study of doses 4, 8 and 16 mg per day. Neurology 1984; 44: 673–680

Outcome

<table>
<thead>
<tr>
<th>Series 1</th>
<th>Series 2</th>
</tr>
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<tbody>
<tr>
<td>Outcome</td>
<td>8 mg</td>
</tr>
<tr>
<td>Improvement in Karnofsky score</td>
<td>60%</td>
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</tbody>
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- Improvement in Karnofsky score
  - 1 week: 50% 51% 50% 50%
  - 2 weeks: 54% 52% 50% 50%
  - 3 weeks: 58% 50% 50% 50%
It is conventional (but not clearly effective) to treat all supratentorial tumors with anticonvulsants before surgery. – *posterior fossa tumors* have low probability of convulsive seizures (no need for anticonvulsants); for *subcortical tumors* prophylactic anticonvulsants are also probably unnecessary. – In general, meta-analysis concluded that no data support use of prophylactic anticonvulsant! 

**PHENYTOIN** is best initial drug (can be continued IV during perioperative period): – start orally (1000 mg* over 12 hours) or IV (1000 mg over 1 hour) → 300–400 mg/d in one dose or split between breakfast and dinner. 

*for children* - 4–8 mg/kg/d 

– periodic blood level checks - keep at free level [1.0–2.0 mg/mL]. 

• if required, patients may be switched easily to alternative oral drugs later.

**OTHER PROBLEMS** 

• no restrictions are placed on activity (patients’ activity relates to overall neurologic status). 

• **ventricular drainage** if *hydrocephalus* is present. 

• **patients with neurologic deficit and immobility** are at risk for deep vein thrombosis & pulmonary embolism - anticoagulation should be considered (recent reports suggest - risk of tumor bleeding with use of anticoagulants is not as high as was once feared, but prophylactic use of anticoagulation is not recommended if patient is not bedridden). 

• **hospice groups** (available in many locations) can be exceedingly helpful in managing *final phase of illness.* 

**SURGICAL TREATMENT** 

see p. Op340 >>

**REOPERATION** 

• is effective for recurrent tumors. 

• directed toward preservation of quality of life during survival. 

• if there is some modality (chemotherapy or brachytherapy) that patient can receive after reoperation, then reresection must be aggressive. 

• tissues are compromised by previous therapy - *postoperative infection* rate is high! 

**LASER (LITT)** 

see p. Op345 >> also see individual tumors 

**RADIOThERAPY** 

about **prINCIPLES, COMPLICATIONS** (incl. radiation necrosis) → see p. Rx11 >>

After surgery, patients* receive full dose radiotherapy. 

*for children < 3 yrs. (age by which myelination is thought to be complete), try to delay radiotherapy or use reduced doses (as compensation use chemotherapy); in *MEDULLOBLASTOMAS* radiotherapy is so effective that it is used in children despite its adverse consequences! 

• radiation therapy is outpatient procedure. 

• timing of radiation therapy - early may be better therapeutically, but brain can be exposed to radiation damage earlier than necessary (tumor cavity stabilizes at 1-2 wk postop). 

• *corticosteroids* for at least 48-72 hours before radiotherapy (dose can usually be tapered relatively early, and often discontinued after 1-2 weeks) 

Target volume varies according to histopathology (also account for patient movement and daily set-up uncertainties).
Radiotherapy with 131I implants for malignant gliomas


Both trials concluded that stereotactic radiation implants do not confer a survival advantage in patients with newly diagnosed malignant gliomas:

Laperriere et al. (1998)
Selker et al. (2002)

Treatment
EBT EBT + 131I Statistical
significance
EBT + 131I BCU
EBT + 131I BCU Statistical
significance

Median
13.2 months
13.8 months
16 months
13.7 months

survival

Currently, attention is turning away from brachytherapy and toward use of stereotactic radiotherapy as technique to increase local tumor doses

PSEUDOPROGRESSION VS. PROGRESSION

• some patients experience transient radiologic deterioration (enhancement volumetric FLAIR signal?) after chemoradiotherapy (14-30% GBMs, 5-24% metastases) mimicking progression:
  a) if GBM had MGMT methylation – it is likely true response – resolves after additional cycles of adjuvant TMZ (i.e. pseudoprogression).
  b) if GBM had unmethylated MGMT – it is more likely a true progression – time to change adjuvant protocol.
  c) in brain metastases treated with monoclonal antibodies – antibodies elicit inflammatory reaction with local increase in BBB permeability

can be differentiated by:

1. RANO criteria - membrane turnover, cell density, and vascularity are increased in glioblastoma – can be detected by:
   1) MRS - increased membrane turnover (high Cho/Cr and Cho/NAA ratios)
   2) DW-MRI - increased cellularity (low ADC)
   3) PW-MRI - high vascularity (high CBV)

2. Detecting increase in circulating tumor cells (in true progression)

3. Experimental MRI techniques - amide proton transfer (APT). MRT, TRAM protocol. see p. Rx11 >>

PATHOPHYSIOLOGY

• most primary CNS neoplasms:
  – are unifocal - potentially curable with local therapy.
  – infiltrate for considerable distance into surrounding normal CNS tissue - need to irradiate substantial amount of normal tissue (tolerance of these tissues becomes limiting factor).
  – radiosensitivity (for conventional radiotherapy):
    *high-dose stereotactic radiosurgery may be effective even for radiosensitive tumors

Radioresistant tumors:
1) PRIMARY CNS LYMPHOMAS
2) PRIMARY NEUROENDOCRINE TUMORS (incl. MELANOCORTISOMAS)
3) GERM CELL TUMORS
4) certain METASTASES (small-cell lung tumor, germ-cell tumors, hematological)

Radioresistant tumors: MENINGOMAS, ACOSTIC NEUROMAS, CHRONITISARCOMAS, GERM CELL TUMORS, certain METASTASES (melanoma, sarcoma, renal-cell carcinoma)

CHEMOTHERAPY

- adjunctive therapy for highly aggressive and infiltrating neoplasms; also for extraneural metastases.
Overall efficacy of antineoplastic drugs in gliomas is only modest!

- chemotherapy usually is administered on INDIVIDUAL basis.
- in children < 3 yrs., chemotherapy is used:
  a) instead of radiotherapy
  b) to compensate for reduced-dose radiotherapy

N.B. full-dose irradiation is only treatment with realistic potential for long-term survival in recurrent disease.

Most chemosensitive tumors:
1. Pilocytic CNS tumors – most sensitive!
2. Oligodendrogliomas – most sensitive of gliomas.
3. MEDULLOBLASTOMAS
4. GERM CELL TUMORS

**CAUSES OF CHEMOTHERAPY FAILURE**

(only ≤ 10% malignant astrocytomas have meaningful and durable responses to chemotherapy):

1. Inadequacy of drug delivery (restricted BBB permeability + slower blood flow in tumors)** → restricts entry of water-soluble drugs → reduces delivery of lipid-soluble drugs

- many intrathecally primary CNS tumors have regions with apparently intact capillaries (actual extent of capillary breakdown accounting for contrast leakage is small). During advancing tumor margins paralyze normal CNS capillaries → abnormal tumor-induced neovessels dominate established tumor areas.
- drugs can be toxic to CNS if given systematically at extremely high doses to circumvent BBB.
- delivering drugs regionally produces greater drug exposure.
- corticosteroids decrease, high-dose radiation increases transcapillary transport of BBB.

**Avoid corticosteroids during chemotherapy!**

2. Tumor cell heterogeneity (i.e. differences in chemosensitivity) → cellular resistance.

3. Inherent resistance, within single tumor multiple mechanisms are operating:

- *P-glycoprotein* - coded by multidrug resistance (*MDR1*) gene (chromosome 7).
- part of BBB - "pumps out" chemicals that are potentially harmful to brain. (nonuniform local mixing)
- present in those of cancer cells and endothelial cells of gliomas.
- little evidence links *MDR1* expression with response to specific chemotherapeutic agents.

**Metabolic resistance**

- Methylation methyltransferase (MGMT) (chromosome 10) - DNA excision repair enzyme - reverses nitrosourea-induced DNA damage (methyl groups inserted into DNA), by catalyzing transfer of methyl group from guanine to its own molecule (since acceptor site is "suicide" enzyme).
- associated with tumor resistance, because it may reverse, in part, impact of alkylating drugs by removing alkyl groups from tumor DNA. 
- Inactivation of MGMT gene in tumor tissue by methylation of promoter region has been associated with good outcomes in malignant gliomas (e.g. methylation of MGMT promoter is strongest predictor for outcome and benefit of temozolomide therapy).

4. Large number of nonproliferating tumor cells (e.g. NEUROBLASTOMAS)

**MEASURES TO ENHANCE EFFECTS**

**HIGH-DOSE SYSTEMATIC THERAPY**
- extremely high doses to circumvent BBB.
- often with autologous bone marrow rescue.
- frequent CNS & systemic toxicity!
- tumors that benefit:
  1) tumor shows sensitivity to conventional-dose treatment.
  2) minimal residual disease after prior therapy.
  3) relapsed disease with minimal or no prior chemotherapy.
  4) pediatric brain tumors.

**REGIONAL THERAPY**

1. Intracarotid therapy (usually by ventricular reservoir).
- for neoplasia in subarachnoid space.
- associated with high morbidity rate - commonly used drugs (methotrexate, cytarabine, thiopeta) produce CNS damage ranging from fever & chills to leukoencephalopathy & myelitis.
- further see p. Onc34

2. Intracarotid infusion

- through carotid or vertebral arteries - increased drug uptake during first passage through tumor capillaries.
- systemic toxicity is almost not reduced (actual amount of drug taken up into tumor is small fraction of injected dose).
- focal brain & retinal toxicity is increased.
- *Place* intracarotid catheter in ICA beyond origin of ophthalmic artery
- drugs that have high systemic clearance but otherwise penetrate tumor well are best candidates (nitrosoureas, cisplatin).
- nonuniform local mixing of drug and blood at infusion site can lead to separate stream within flow of vessel ("streaming").

**N.B. intracarotid BCNU lessens survival over that afforded by intravenous BCNU**

3. Intratumoral therapy
- for cystic tumors with narrow rim of surrounding tumor.

4. Convection-enhanced delivery (CED) - high-pressure microinjection with intracavitary (either intraarterial or percutaneous catheter)
- allows for direct delivery and wide local distribution of highly concentrated therapeutics
- most frequently, used for biotoxin ligated to drug delivery system.

**BBB disruption**
- reversible opening of BBB with intracavitary hyperosmolar infusions:
  a) nonselective - MANNITOL, ARABINOSE - rapid intra-arterial injection under general anesthesia
  b) selective - NITRIC OXIDE, BRADYKININ-2 ANALOGS.
- successful alternative – focused ultrasound (FUS). see p. Rs 15.7
- can enhance penetration of different compounds of various sizes, molecular weights, and liposolubility (increased drug levels in CNS have been documented).
- produces far greater increase into normal brain tissue, rather than tumor → enhanced CNS toxicity (similar to regional therapy).
leukoencephalopathy C4 increases vascular permeability in systemic capillary beds and brain tumors but has little effect on normal brain capillaries.

other unsuccessful approaches for BBB disruption - dimethyldisulfide, hypencapnia, low-dose ionizing or microwave radiation.

**DIFFERENTIATION THERAPY**

- differentiating agents may induce differentiation and suppress growth of tumors (incl. GLIOMASTOMA MULTIFORME, MEDULLOBLASTOMA).

1. RETINOIC ACID - modulates autocrine growth loops, inhibits kinase activity of epidermal growth factor receptor.

2. PHENULETACETATE - DNA hypomethylation with secondary alterations in cycle-regulatory proteins.

**DRUGS**

- must have ability to cross BBB (esp. for peripheral areas of tumor in which BBB is relatively intact).

All non-sugar-containing chloroethylnitrosoureas (CENUs) can cross BBB: 1) LOMUSTINE (CCNU) 2) PCNU 3) NIMUSTINE (ACNU) 4) SPIRODMUSTINE - designed specifically for gliomas. 5) CARBONUSTINE (BCNU) - most effective and most frequently used drug for HUMAN ASTROCYTOMAS.

- specific form - Glaidel® implant (polidroprosan 20 with carmustine) - slow release (over 2-3 years). carmustine is stereoselectively implanted biodegradable polymer wafers; up to 8 Glaidel wafers are implanted in cavity (modest benefit).

- dura must be closed water tight (may place overlay DuraGuard) or will lead to wound breakdown.

Adjuvant localized chemotherapy (carmustine wafers) for malignant gliomas

Bren H et al., for the Polonno-Brain Tumor Treatment Group. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery of biodegradable polymers of chemotherapeutic for recurrent gliomas. Lancet 1993; 343: 1008 – 1012.


**CARBOPlatin -** most active platinuming agent.

- PACLITAXEL, POLIQUELIN (Opaxio) - FDA granted orphan drug status for treating GBM, it is "biologically enhanced chemotherapeutic that links paclitaxel to biodegradable polylactate polymer, resulting in new chemical entity: improved delivery of paclitaxel to tumor tissue while protecting normal tissue from toxic side effects."

**Standard therapies:**

A) CARBOMUSTINE - drug of choice for malignant gliomas.

B) PCV combination (POPCARBAZINE, LOMUSTINE, VINCRISTINE) - unusually beneficial against OLIGODENDROGLIOMAS.

**TEMZOLOMIDE (Temodar®)** - oral alkylating agent.

- prodrug - rapidly spontaneously hydrolyzed to active 3-methyltriazen-1-yl methylazolo-4-carboxamide (MTIC).

- mechanism of action - DNA alkylatation (methylating mainly at O6 and N7 positions of guanine).

- oral capsule: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg.

- rapidly and completely absorbed after oral administration (100% bioavailable).

- 35% crosses BBB.

- rapidly eliminated (T1/2 = 1.8 hr).

- drug interactions: VALPROIC ACID decreases clearance of temozolomide by 5%.

- indications:

  1. adults with newly diagnosed GLIOMASTROMA MULTIFORME concomitantly with radiotherapy = maintenance for additional 6 months = STUPP protocol => N.B. prophylaxis against Pneumocystis carinii pneumonia is required for all patients.

  2. adults with refractory ACANTHOMASTROMA (i.e. disease progression on regimen containing NITROSOUREA and PROCARBAZINE).

- adverse reactions:

  1. nausea & vomiting – most common adverse events (H: premedicate with ZOPIAN).

  2. fatigue, headache.

  3. convulsions.

  4. myelosuppression (esp. women and elderly) – prior to dosing, patients must have absolute neutrophil count (ANC) > 1.5 x 10^9 and platelet count > 100 x 10^9 / L => CBC on day 21 (2 days after first dose) and weekly until ANC is above 1.5 x 10^9 and platelet count exceeds 100 x 10^9.

  5. infections: DIAPRESO 100 mg for Pneumocystis carinii prophylaxis.

  6. initiation of GMCSF given in tumor tissue by methylating the strongest predictor for outcome and benefit of temozolomide chemotherapy, see above =>

- “Temozolomide” trial


- DXT alone vs. DXT + temozolomide.

- class I evidence (573 patients, 85 centers in 15 countries).

- 86% of patients underwent debulking surgery.

- 60 Gy in daily 2 Gy fractions over 6 weeks (5 days per week).

- daily temozolomide (75 mg/m²/day) for the duration of the radiotherapy – 6 adjuvant cycles of temozolomide (150-200 mg/m²) for 5 days during every 28-day cycle.)
IMMUNOTHERAPY

NB. CNS is immunologically isolated from immune effectors (disruption of barrier in tumors may still be insufficient to mount true response).

1. BIOLOGIC IMMUNE RESPONSE MODIFIERS – VARIOUS CYTOKINES (interferons, interleukins, tumor necrosis factor, growth factors) - demonstrate growth-inhibitory and cytotoxic responses in glioma cell lines.

2. ADAPTIVE IMMUNOTHERAPY (IL-2 administration with lymphokine-activated killer [LAK] cells or tumor-infiltrating lymphocytes [TILs]) - in vitro activity against gliomas; cerebral edema induced by local inflammatory response remains problem.

3. MONOCLONAL ANTIBODIES (mAb)
   - only few tumor-specific proteins have been identified (translated form of EGFR represents unique tumor antigen on gliomas cell's surface).
   - most useful clinically are antibodies capable of detecting oncospecific proteins in tumor tissue.
   - two potential mechanisms:
     a) inhibition of growth-stimulatory receptor by binding of mAb.
     b) conjugating mAb to cytokine agents (drugs, radioactive isotopes, toxins).
   - has many problems:
     1) BBB is sufficiently intact to prevent easy penetration of large-molecular-weight substances (H: BBB disruption, intracathal application).
     2) tumor heterogeneity.
     3) rapid immune antibody clearance (H: human-derived antibodies, chimeric mAbs/mouse/human constructs).
     4) dehalogenation - loss of radionuclides (H: nonhalogen radionuclides, immunotoxin-conjugated monoclonal antibodies).
     5) excessive radiation to nontarget reticuloendothelial, hepatic, and renal tissues.

4. DIRECT INTRATUMORAL BACTERIAL INJECTION

MOLECULAR SIGNATURES OF Glioblastoma Multiforme - present in all GBM cases, but not in normal CNS: i.e. common molecular denominators of GBM.

- therapeutic agents are delivered locoregionally (stereotactic catheter) - convection-enhanced delivery.
- median survival increased to 360 days (vs. 84 days with Gliadel).

1. IL-13 receptor type 2b (IL-13Rα2) - gene is found in 100% GBM cases; protein expressed only in 75%; therapeutically used ligand – IL-13 conjugated with Diphtheria toxin.

2. Ephrin A2 - type of tyrosine kinase in cell signaling pathways; therapeutically used ligand - Eph A2 conjugated with Pseudomonas toxin.

3. Fra-1

4. Tenascin C - abundant extracellular matrix protein not expressed on normal brain; therapeutically used anti-tenascin antibody RICs - is bonded to 111In and injected into surgical cavity (RADIONUCLIDEIMMUNOTHERAPY); dose 44 Gy is optimal.

GENETIC THERAPY

- see also p. 3788

- extensive tumor heterogeneity - which gene(s) is to be targeted?
- all cells in tumor must be altered while sparing normal cells.
- neurons are nondividing cells and are therefore resistant to viral vectors that infect only dividing cells.

ANTISENSE REAGENTS

- pairing with complementary strand of nucleic acid - specific disruption of target gene expression.
Three different classes:
1. Antisense oligodeoxynucleotides (ODNs) - short nucleotide sequences (usually < 30 nucleotides) complementary to target mRNA; effects are transient, unless ODNs are supplied continually to cells.
2. Antisense RNA; common production route is introduction of encoding antisense DNA gene into cultured cells or germ lines.
3. Ribozymes - antisense RNAs that also have enzyme activity (cleave RNAs at preselcted sites).

**GENE THERAPY**

- **gene transfer** (single gene could modify tumorigenic properties of cells).thestandard as a clinical trial endpoint for GBM is 6 months progression free period:
- Intracranial tumors

**2. Suicide gene therapy** - transduction of gene that converts pro-drug into toxic substance → "bystander effect" (i.e. killing of adjacent tumor cells by transfer of activated drug).

a) E. coli cytosine deaminase converts 5-fluorocytosine (5-FC) into 5-FU.

b) herpes simplex thymidine kinase (HSV-tK) phosphorylates ganciclovir, thus inhibiting DNA synthesis and killing cell (bystander effect is mediated through gap junction transport of nonphosphorylated ganciclovir to nontransduced cells, and when nontransduced cells endocytose debris containing phosphorylated ganciclovir from dying cells).

- *e.g.* fibroblasts neurosurgically inserted into tumor bed

**3. Immunomodulatory gene therapy** - provokes cellular immune responses; tumor vaccine, suspension of irradiated tumor cells that are transfected with cytokine gene, is injected into skin to stimulate systemic immune response against tumor-specific antigens (there are few tumor-specific antigens and it appears to work only against low tumor burden).

- vehicle of greatest interest in delivering foreign genes into tumor cells is retrovirus.

**TREATMENT ACCORDING TUMOR TYPE**

**HIGH-GRADE ASTROCYTOMAS** - (partial) resection + irradiation + chemotherapy.

**LOW-GRADE ASTROCYTOMAS** - surgery + irradiation (uncommon if completely resected) ± chemotherapy.

**OLIGODENDROGLIOMAS**

- a) observation
- b) surgery ± irradiation (uncommon if grossly completely resected) ± chemotherapy.

**EPENDYMOMAS** - surgery + irradiation (to whole CNS, if CNS seeding); chemotherapy for recurrences.

**MEDULLOBLASTOMAS** - surgery + whole CNS irradiation ± chemotherapy.

**HEMANGIOBLASTOMAS**

- a) observation
- b) complete surgical resection (if not complete ± + irradiation)

**MEINGIOMAS** (radioreistant) - usually surgically removable vs. stereotastic radiation.

**SCLERORRHECTASIA** - (surgical removal +) whole brain irradiation.

**MULTIPLE MEINGIOMAS** - whole brain irradiation ± chemotherapy.

**LYMPHOMA** - unusually sensitive to radiation & chemotherapy; surgery has no role!

**PETITARY ADENOMAS** - treatment depends on tumor size and hormonal activity:

- a) observation, medical treatment
- b) surgery ± irradiation

**CRANIOPHARYNGIOMAS**

- a) total surgical resection
- b) subtotal surgical resection → irradiation

**PITUITARY TUMORS** - surgery ± whole brain irradiation.

**NORRISEROMATOUS GERM CELL TUMORS** - chemotherapy → radiation.

**EPIDERMAL DERMATOMAS** - surgery.

**ACOUSTIC NEURINOMAS, PARSANGIOMAS**

- surgery ± stereotastic irradiation (unnecessary if completely resected)
- b) stereotastic irradiation
c) observation

**PREGNANCY**

Intracranial tumors compressing optic apparatus that present during pregnancy or in early postpartum period:

- a) no visual deterioration → treat conservatively
- b) visual deterioration in the first or second trimester → neoursurgical procedure during pregnancy with delay
c) visual deterioration during the third trimester may also be treated surgically however it carries a high risk for preterm delivery: visual deterioration at 34 weeks or later should be considered for urgent C-section before neurosurgical intervention.


**FOLLOW UP**

Astrocytoma - see p. Onc10 >>

- **minimal residual disease** - hematology term - HemOnC routinely does bone marrow samplings and still find leukemia cells even if patient is in clinical remission; should we do this for brain tumor patients?; at least at recurrence, (in the future) patient should be biopsyed to find new targetable mutations.

**PROGNOSIS**

Extra-axial neoplasm implies more favorable prognosis than does intra-axial location.

**MEDIAN SURVIVAL**

**LOW-GRADE ASTROCYTOMAS** - 7.5 yrs. (5-yr survival 25% with surgery alone, 50% with surgery + radiotherapy).

**HIGH-GRADE ASTROCYTOMAS** - 5-yr survival 85% (by other data, 10-yr survival > 90%); even with partial resection median survival > 8 yrs.

**BRAIN STEM GLIOMAS** - survival of only months.

**HIGH-GRADE ASTROCYTOMAS** - 40-1 yr survival (25% patients survive 2 yrs):

- ANAPLASTIC ASTROCYTOMA - 18-24 months (1.5-5 yrs).
- GLOBEASTOMAS MULTIFORME - 10 months (14 weeks with surgery alone, 40 weeks with surgery + radiotherapy, 9.4 mos with chemoradiation alone); 5-yr survival < 5%.

The current gold standard is a clinical trial endpoint for GBM in 6 months progression free survival.
Online calculator for the Prediction of Survival in Glioblastoma Patient: https://cnoc-bwh.shinyapps.io/gbmsurvivalpredictor/  

**Favorable prognostic variables:**  
1) **lower tumor grade** – most important!   
2) **certain genetic characteristics**; e.g. IDH-mutant gliomas have more favorable prognosis than IDH-wildtype and it applies to both grade II and grade III tumors. See p. Onc10 >>   
3) **young age (< 45 yr)** – second most important!   
4) **better clinical status** (Karnofsky performance index)   
5) **little or no residual tumor** after initial resection (prognosis is worse for midline tumors - aggressive resections are difficult).

On Cox-regression analysis, cerebellar tumor location independently predicted poor prognosis in pediatric patients with high-grade glioma (HGG):  
— median overall survival in patients with cerebellar HGG vs. those with cortical HGG (0.92 years vs. 2.03 years); similar for cerebellar GBM (0.9 year vs. 1.53 years)  
— median event-free survival is non-significantly shorter with cerebellar HGG (0.62 year vs. 0.91 year); similar for cerebellar GBM (0.53 year vs. 0.66 year)

Survival in astrocytomas:  

**PATIENT CLASSES**  
**Memorial Sloan Kettering recursive partitioning analysis (RPA) classes:**  
class 1 (patients < 50 yr old)  
class 2 (patients ≥ 50 yr old with KPS ≥ 70)  
class 3 (patients > 50 yr old + KPS < 70)  

**BIBLIOGRAPHY** for ch. “Neuro-Oncology” — follow this LINK >>