Treatment planning demands tissue diagnosis!

Final goal of therapy - CYTOREDUCTION: decrease of total tumor mass to size that immune system might suppress and eventually kill (for gliomas it is $0.0001\ g$, or $1 \times 10^{-7}$ cells).

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

1. **surgery** - usually leaves residual tumor burden of 1-5 x $10^3$ cells; surgical procedure removes tumor cells or 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).

   - if tumor bulk is reduced, quiescent cells enter active growth phase, making them more susceptible to radiotherapy.

2. **radiotherapy** might kill two additional logs of cells, reducing tumor to $1 \times 10^3$ cells;

3. **chemotherapy** must then kill two additional logs to reduce burden to desired $1 \times 10^3$ cells.

   - current chemotherapies produce net cell kill of only about 1 log and thus tumor grows despite drug administration.

   Present-day multimodality therapy 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**

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

   - small MENINGIOMAS or ACOUTIC NEUROMAS usually do not require treatment to reduce ICP.

   - **Dexamethasone** is steroid of choice (lowest mineralocorticoid activity, best CNS penetration).

**Dose** - start with oral loading dose of 10-24 mg $\rightarrow$ 4-10 mg x 4/d (or $x \times 2$).

   - for children - start $0.5-1$ mg/kg $\rightarrow$ 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 dose** that maintains patients at maximum level of comfort and function should be sought (decrease dosage until symptoms increase or become apparent $\rightarrow$ increase dosage until they subside);

   - N.B. tumor growth or treatment-induced effects may require dosage?; decrease in steroid requirement suggests improvement.

   - antilucre agent (e.g. H3-blocker) and glycemia control (e.g. insulin on sliding scale) are required.

---

**LOW-DOSE VERSUS HIGH-DOSE DEXAMETHASONE IN METASTATIC BRAIN TUMORS**

Vecht CJ et al. Dose-response 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: 475 – 480

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Series 1</th>
<th>Series 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mg</td>
<td>16 mg</td>
<td>Statistical significance</td>
</tr>
<tr>
<td>4 mg</td>
<td>16 mg</td>
<td>Statistical significance</td>
</tr>
<tr>
<td>Improvement in Karnofsky score</td>
<td>4 weeks</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>4 weeks</td>
<td>53%</td>
</tr>
</tbody>
</table>
After surgery, patients receiving 16 mg/day had approximately 25% improvement on proximal muscle weakness in the first month there was no significant improvement in the subsequent month.

- patients receiving 4 mg/day experienced < 50% of the number of Cushingoid faces as those receiving 16 mg/day (p = 0.03).
- there were no significant differences in the improvement of Karnofsky scores between dosing regimens at 1 week or any other time point.
- after 1 week, 4 mg is as effective as 16 mg of dexamethasone in patients with no impending signs of brain herniation.
- tic effects of dexamethasone are dose dependent and are much more frequent if 16 mg is administered for prolonged periods (> 1 month).

- study recommendations:
  - Neurological status of patient
  - Dosing regimen
  - LCS or signs of TICP
  - pending herniation
  - GCS 15/15 or no signs of TICP
  - 10 mg IV stat + 4 x 4 mg/day orally
  - 4 mg/day orally

- tapering over 4 weeks.

In instances of extreme intracranial pressure, speed and action of dexamethasone are not sufficient – add MANSTIN, see p. 530 +

- it is unusual for patients to decompensate preoperatively so severely that intubation becomes necessary (nevertheless, this does occur).

N.B. injudicious use of 5% dextrose IV (hyposmolar) or hypnorm (result in hyperventilation → hypercarbia) often is sufficient to produce abrupt increase in brain edema and herniation.

SEIZURES

- 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!

PHENTYLAN 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 [1-2.0 mg/mL].
  - if required, patients may be switched easily to alternative oral drugs later.

PSYCHIATRIC PROBLEMS

- some patients derive tremendous help from each other in organized support groups.
- depression is often significant problem → appropriate pharmacotherapy.
- fatigue is common (esp. during and after radiotherapy) → stimulants, PEMoline, PROprXYLINE.

OTHER PROBLEMS

- no restrictions are placed on ACTIVITY (patients’ activity relates to overall neurologic status).
- ventricular drainage (Hydrocephalus) is present.
- patients with neurologic deficit and immobility are at risk for deep vein thrombosis & pulmonary emboli - 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

- HEMATOMA

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 resection must be aggressive.
- issues 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 myelinization is thought to be complete), try to delay radiotherapy or use reduced doses (as compensation use chemotherapy); in MEDULLOBLASTOMAS radiotherapy is so effective that 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).
- ster 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):
Most chemosensitive tumors

Overall efficacy of antiradiosensitive tumors

Pathophysiology

- most primary CNS neoplasms:
  - are unifocal - potentially curable with local therapy.
  - infiltrate for considerable distance into surrounding normal CNS tissue - need to irradicate 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 radioresistant tumors

Radiotherapy with IT bolus implants for malignant gliomas

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EBRT</th>
<th>EBRT + IT bolus</th>
<th>Statistical significance</th>
<th>175 Gy + EBRT</th>
<th>EBRT</th>
<th>BCNU</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>months</td>
<td>13.2</td>
<td>13.8</td>
<td>None (p = 0.49)</td>
<td>16</td>
<td>16 months</td>
<td>None (p = 0.10)</td>
</tr>
</tbody>
</table>

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

Radiosurgical solutions

- may be placed into cystic cavities.

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

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

Most chemosensitive tumors

1) PRIMARY CNS LYMPHOMAS – most sensitive!
2) OLIGODENDROGLIOMA – most sensitive of gliomas.
3) MEDULLOBLASTOMA
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)
2. Damage to vital brain structures leaves little reserve for chemotherapy (H: colony-stimulating factors)
2. Tumor cell heterogeneity (i.e. differences in chemosensitivity) → cellular resistance.

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

- Polydrug resistance - coded by multidrug resistance (MDR1) gene (chromosome 7).
  - part of BBB - “pumps out” chemicals that are potentially harmful to brain.
  - present in membrane of cancer cells and endothelial cells of gliomas.
  - little evidence links MDR1 expression with response to specific chemotherapeutic agents.

- Methylamine/methylester transferase (MGMt) (chromosome 10) - DNA excision repair enzyme - repairs nitrosourea-induced DNA damage (methyl groups inserted into DNA), by catalyzing transfer of methyl group from guanine to its own molecule (since acceptor site cannot be regenerated, MGMt is “suicide” enzyme).
  - associated with tumor resistance, because it may reverse, in part, impact of alkylating drugs by removing alkyl groups from O6 position of guanine.
  - inactivation of MGMt gene in tumor tissue by methylation of promoter region has been associated with good outcomes in malignant glioma (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. NEUROBLASTOMA).

MEASURES TO ENHANCE EFFECTS

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

2. Intraarterial 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), and local brain & retinal toxicity is increased.
   - see below

   - place intraarterial 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 vessel (“streaming”).

   N.B. intra-arterial 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 microinfusion with intracranial (either intratumoral or peritumoral) catheter.
   - allows for direct delivery and wide local distribution of highly concentrated therapeutics.
   - most frequently, used for biotin ligated to drug delivery systems.

BBB DISRUPTION
- reversible opening of BBB with intracranial hypersmolar infusions
  a) nonselective - VANCOMYCIN, AMIKIN - rapid intr-arterial injection under general anesthesia.
  b) selective - NITRIC OXIDE, BRADYKININ-2 ANALOGS.
   - successful alternative - focused ultrasound (FUS), see p. 155 >
   - 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 of entry into normal brain tissue, rather than tumor → enhanced CNS toxicity (similar to regional therapy).
   - leptomeninge 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 - dimethylsulfoxide, hypercapnia, low-dose ionizing or microwave radiation.

DIFFERENTIATION THERAPY
- differentiating agents may induce differentiation and suppress growth of tumors (incl. GLIOBLASTOMA multiforme, MEDULLOBLASTOMA).
  1. RETINOIC ACID - modulates autocrine growth loops, inhibits kinase activity of epidermal growth factor receptor.
  2. PHENYLACETATE - 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 chloroethylnitrosourea (CENUs) can cross BBB:

1) LOMUSTINE (CCNU)
polymer, resulting in new chemical entity; improved delivery of paclitaxel to tumor tissue while "biologically enhanced chemotherapeutic that links paclitaxel to biodegradable polyglutamate.

Adjuvant localized chemotherapy (carmustine wafers) for malignant gliomas

Bonn RB et al., for the Pelmat-Horn Tumor Treatment Group. Plaque-controlled trial of safety and efficacy of concomitantly delivered biodegradable polyglutamate wafer, up to 8 Glial wafers are implanted in cavity (modest benefit).

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

class I evidence.

carmustine versus placebo

PTT with treatment GBM requiring reoperation: no statistically significant effect of carmustine wafers.

GSG trial (newly diagnosed GBM); benefit from carmustine wafers.

DIAZEPOME (AZT) - designed specifically for gliomas.

CARBOPlatin - most active platinum agitating agent.

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

Standard therapeutics:

A) carmustine - drug of choice for malignant gliomas.

B) PCV combination (PROCARZINE, LOMUSTINE, VINCristine) - unusually beneficial against Oligodendroglialomas.

TEMOZOLOMIDE (Temodar®) - oral alkylating agent.

- produrg - rapidly spontaneously hydrolyzed to active 3-methyltriazene-1-yl imidazole-4-carboxamide (MTIC).

- mechanism of action – DNA alkylation (methylation mainly at O6 and N7 positions of guanine).

oral capsules: 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 Glioblastoma 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 recurrent gliosarcoma (i.e. disease progression on drug regimen containing Nitrosourea and Procarzine).

adverse reactions:

- nausea & vomiting – most common adverse events (H: premedicate with ZOPINAS).

- fatigue, headache.

- convulsions.

- myelosuppression (esp. women and elderly) - prior to dosing, patients must have absolute neutrophil count (ANC) > 1.5 x 10⁹ and platelet count > 100 x 10⁹. ↓ CBC on day 22 (21 days after first dose) and weekly until ANC is above 1.5 x 10⁹ and platelet count exceeds 100 x 10⁹.

- infections: DIAZEPOME 100 mg/d for Pneumocystis carinii prophylaxis.

- inactivation of MGMT gene in tumor tissue by methylation is the strongest predictor for outcome and benefit of temozolodim chemotherapy.

- ‘Temozolodim trial’

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DIAZEPOME (AZT) - anti-VEGF monoclonal antibody.

- FDA approved for recurrent GBM see for Caudin agent: p. (Oct/11).

- VEGF is also known as vascular permeability factor! - anti-VEGF therapy decreases tumor enhancement on imaging!!

- adverse effects:
COMPLICATIONS

1. acute encephalopathy
2. chronic leukoencephalopathy (bilateral periventricular white matter lesions)
3. stroke-like episodes
4. cerebellar syndrome

- toxicity depends on
  1) dose
  2) route of administration
  3) prior radiotherapy (increases BBB permeability), e.g. methotrexate after radiotherapy!!!

- clinical worsening may occur early in therapy (at least 10% patients) from increase in tumor bulk resulting from effective therapy
  1) cell mass increase when doomed cells form giant cells or undergo one or more successful cell divisions before dying.
  2) edema induced by irritative products of cell lysis.
  3) CNS has inefficient mechanism for disposing of dead cells.

IMMUNOTHERAPY

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. ADOPTIVE IMMUNOTHERAPY (HL-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 (truncated form of EGFR represents unique tumor antigen on glioma cell surface).

- most useful clinically are antibodies capable of detecting oncogenic proteins in tumor tissue.

- two potential mechanisms:
  a) inhibition of growth-stimulatory receptor by binding of mAb.
  b) conjugating mAb to cytotoxic agents (drugs, radioactive isotopes, toxins).

- has many problems:
  1) HBb is sufficiently intact to prevent easy penetration of large-molecular-weight substances (H: BBB disruption, intrathecal application).
  2) tumor heterogeneity
  3) rapid immune antibody clearance (H: human-derived antibodies, chimeric mAbs [mouse/human constructs]).
  4) dehalogenation → loss of radionuclides (131I): (H: nonhalogen radionuclides, immunotoxin-conjugated monoclonal antibodies).
  5) excessive radiation in 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 a2 (HL-13Rd) - gene is found in 100% GBM cases, but protein expressed only in 75%; therapeutically used ligated - HL-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 131I and injected into surgical cavity (RADIOIMMUNOTHERAPY); dose 44 Gy is optimal.

GENETIC THERAPY

- 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 inhibit only dividing cells.

ANTISENSE REAGENTS
- pairing with complementary strand of nucleic acid → specific disruption of target gene expression.

Three different classes:
1. antisense oligodeoxynucleotides (ODN) - short nucleotide sequences (usually < 30 nucleotides) complementary to target mRNA; effects are transient, unless ODNs are supplied continually to cell(s).
2. antisense RNAs, common production route is introduction of encoding antisense DNA gene into cultured cells or germ line.
3. ribozymes - antisense RNAs that also have enzyme activity (cleave RNAs at preselected sites).

IMMUNOTHERAPY

also see p. 1675 (8) >>

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

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GENE THERAPY

• gene transfer (single gene could modify tumorigenic properties of cells).

1. Tumor-suppressor gene therapy - replacement with correct copy of gene whose mutation initiates or significantly alters malignant phenotype (e.g. transduction of cancer cells with p53).

2. Suicide gene therapy - transduction of gene that causes pro-drug to toxic substance → "bystander effect" (i.e. killing of adjacent tumor cells by transfer of activated drug).
   a) E. coli cytochrome deaminase converts 5-fluorouracil (5-FU) 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 nonfluorescent phosphorylated GCV to nontransduced cells, and when nontransduced cells endocytose debris containing phosphorylated GCV 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 transduced 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.

PSEUDOPROGRESSION vs. PROGRESSION

• some patients experience transient radiologic deterioration (enhancement volume?, FLAIR signal?) after chemoradiotherapy (14-30% GBMs, 5-24% metastases) mimicking progression:
   a) if GBM had MGMT methylation – it is likely a sign of 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 (response assessment for neuro-oncology) criteria - membrane turnover, cell density, and vascularity are increased in glioblastoma – can be detected by:
   • 1-HMR - increased membrane turnover (high Cho/Cr and Cho/NAA ratios)
   • DW-MRI - increased cellularity (low ADC)
   • PM-MRI - high vascularity (high Cho BV)

2. iRANO (immunotherapy response assessment for neuro-oncology) criteria - modification of RANO criteria to address the challenges of novel immunotherapy (vs. routine chemo-radiotherapy Stupp protocol) for high-grade gliomas:
   • immunotherapy does not result in pseudoprogression.
   • key differences from RANO:
     1) new enhancing lesion outside the main radiation field are encountered in immunotherapy and therefore do not automatically denote progressive disease in iRANO.
     2) onset of immunotherapy effect can be delayed - iRANO requires a repeat scan (3 months later) to confirm disease progression
   • progressive disease can be diagnosed in the setting of immunotherapy in the following scenarios:
     a) significant clinical deterioration (not attributable to other non-tumor causes and not due to steroid decrease)
     b) > 6 months of immunotherapy – same as RANO imaging criteria
     c) ≤ 6 months of immunotherapy - requires a second scan confirming further progressive disease 3 months after the initial scan showing features of progressive disease (during this interval, immunotherapy can continue! if toxicity is minimal)
   *do not give steroids – will defeat purpose of immunotherapy!!!

3. Detecting increase in circulating tumor cells (in true progression)
   4. Experimental MRI techniques - ane proton transfer (APT) MRI, TRAM protocol. see p. Rx11

TREATMENT ACCORDING TUMOR TYPE

HIGH-Grade astrocytomas: (partial) resection + irradiation + chemotherapy.
LOW-Grade astrocytomas: surgery ± irradiation (unnecessary if completely resected) ± chemotherapy.
Oligodendrogliomas:
• a) observation
• b) surgery ± irradiation (unecessary if grossly completely resected) ± chemotherapy.
Ependymomas - surgery ± irradiation (to whole CNS, if CSF seeding); chemotherapy for recurrences.
Medulloblastomas - surgery ± whole CNS irradiation ± chemotherapy.
Hemangioblastomas:
• a) observation
• b) complete surgical resection (if not complete = + + irradiation)
Meningiomas (radiosensitive) – usually surgically removable vs. stereotactic radiation.
Single metastases – (surgical removal ±) whole brain irradiation.
Multiple metastases – whole brain irradiation ± chemotherapy.
Lymphomas – unusually sensitive to radiation & chemotherapy; surgery has no role! 
PITUITARY 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
Pinealomas, MATURE TERATOMA - surgery.
Pineoblastomas – surgery → radiation ± chemotherapy.
GERMINOMAS – radiation.
Nongerminomatous GERM CELL TUMORS - chemotherapy → radiation.
EPENDYMOMS, DERMoids – surgery.
ACOUSTIC NEUROMA, PARAGANGLIA:
• a) surgery to induce irradiation (unnecessary if completely resected)
• b) SRS
• c) observation

PREGNANCY

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

• d) no visual deterioration – treat conservatively
• e) visual deterioration in the first or second trimester → neurosurgical procedure during pregnancy without delay
BRAIN TUMORS (treatment)

FOLLOW UP

Astrocytomas — see p. Onc10 >>
- minimal residual disease — hematology term — HemOnc routinely does bone marrow samples 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 biopsied to find new targetable mutations.

PROGNOSIS

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

Median survival:
- LOW-GRADE ASTROCYTOMA — 7.5 yrs. (5-yr survival 25% with surgery alone, 50% with surgery + radiotherapy).
- JUVENILE Pilocytic astrocytoma — 5-yr survival = 85% (by other data, 10-yr survival > 90%); even with partial resection median survival = 8 yrs.
- BRAIN STEM GLIOMA — survival of only months.
- HIGH-GRADE ASTROCYTOMA — 40% 1-yr survival (25% patients survive 2 yrs): ANAPLASTIC ASTROCYTOMA = 18-24 months (1.5-5 yrs). GLOBLASTOMA MULTIFORME = 18 months (14 weeks with surgery alone, 40 weeks with surgery + radiotherapy, 9.4 mos. with chemotherapy alone); 5-yr survival < 5%.

The current gold standard as a clinical trial endpoint for GBM is 6 months progression-free survival.


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 pediatrics 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 years vs. 1.53 years)
- median event-free survival is non-significantly shorter with cerebellar HGG (0.62 years vs. 0.91 years), similar for cerebellar GBM (0.53 years vs. 0.66 year)

Survival in astrocytomas:

Mean Survival (months)

Low Grade
Grade III
Grade IV (GB)
WHO Grade Tumor

34
113
142

Subtotal Resection
Gross Total Resection

Patient Classes

Memorial Sloan Kettering recursive partitioning analysis (RPA) classes:
BRAIN TUMORS (TREATMENT)

Onc3 (9)

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