Neuro-Oncology 2025: What's New in Brain Tumor and Practical Tips in the Management of Neuro-Oncology Patients



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Disclosure

- Consultant/Research funds: UCB
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- NIH/NCI RO1 and U01 Funding
- Podcast Host for NI CCF: Consult QD and search under Neurosciences, If Apple or Spotify, just search "Neuro Pathways" to get to it.
- One final disclosure

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Canada's Finest

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Objectives

1. Review common brain tumors and treatments
2. Review the role of anti-seizure medication (ASM) and steroid use in brain tumor patients
3. Discuss guidelines and best practices for supportive care of brain tumor patients

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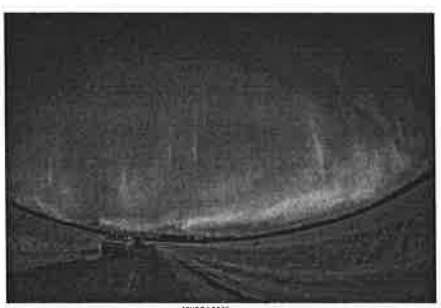
Thought I would never see it:



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vHL: Belzutifan: blocks hypoxia-inducible factor (HIF-2α)- game changer?

A. Dhawan, D.M Peereboom, G.H.J. Stevens. First clinical experience with belzutifan in von Hippel-Lindau disease-associated CNS hemangioblastoma. Accepted to CNS Oncology July 2022

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https://www.futuremedicine.com/doi/full/10.2217/cns-2022-0006

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Case Example

- 36 y/o RHM to OPD for tx options for recently dx astrocytoma
- May had problems expressing himself
- June/July inappropriate behavior
- MVA July 12th (probable complex partial seizure (CPS))
- Next wk R hand tingling, expressive speech problems
- CT/MRI LF mass (came only w preop CT)
- s/p STR July 17th at outside facility- no post op MRI
- Pathology: anaplastic astrocytoma (new WHO has removed)
- Steroids DC 3 days post op
- On phenytoin (PHT) for probable sz

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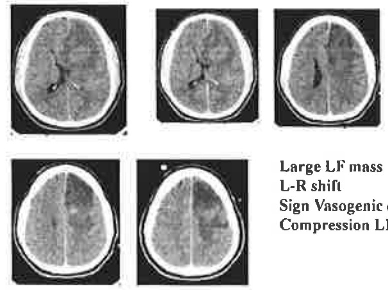

Large LF mass
L-R shift
Sign Vasogenic edema
Compression LF horn

CT Brain w/o preop: NO post op scan completed!

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Postop MRI's

- Complete a post op MRI w/i 48 hours of surgery
- why? Decreased artifact, need to compare tx affect
- >48 hours: increased artifact

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Recent Case From Brain Tumor Conference – another outside case

PREOP: Axial T1 +GAD

Post op w/o GAD 2 wks later

Post op w GAD Enhancement related to DWI changes

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Postop MRI

- Prospective study 60 high grade glioma patients
- Serial CT/MRI 1 to 5 days postop
- GAD MRI helpful if performed w/i 1-3 days postop
- Limited surgically induced enhancement and minimized interpretive difficulties
- MRI superior to CT scan
- Evaluated surgeons impression of resection vs. imaging findings of degree of resection
- Neurosurgeons estimate less accurate than postop imaging by a factor of 3

Albert F, et al Neurosurgery 1994;34:45-61

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ASM: Phenytoin

- Still the go to drug for some neurosurgeons?
- Most now using Levetiracetam (Keppra) at our Institution
- Generic vs. brand name dosing for PHT
- Understand the kinetics MM- nonlinear
- Monitor free vs. bound
- Comfort and IV formulation

- FDA warning in 2008 on suicidality and ASM use

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Phenytoin

- 1998 FDA approved generic PHT capsule (Parke-Davis)
- State Minnesota: B to G switch w/o physician notification
- 8 patients w increased sz after conversion to generic PHT
- Mean reduction of 13% in bioavailability to brand name
- xPHT brand name: 17.7mg/L vs. 12.5mg/L w generic
- Have to ask patients what they are taking

Burkhardt et al Lower phenytoin serum levels in persons switched from brand to generic phenytoin. Neurology 2004;63:1494-1496

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Seizures and Brain Tumors

- ~200,000 Metastases dx per year
- ~60,000 Primary tumors dx per year
- ~20-40% seizure prior to or after initial dx (depends on tumor type and grade and risk could be 80% or more)
- Should everyone go on anti-seizure medication?

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Practice Parameter from the AAN

- Anticonvulsant prophylaxis in patients with newly diagnosed brain tumor. Report of the Quality Standards Subcommittee of the American Academy of Neurology.
- M.J.Glantz, B.F. Cole, P.A. Forsyth, L.D. Recht, P.Y. Wen, M.C. Chamberlain, S.A. Grossman, and J.G. Cairncross. Neurology. 2000; 54:1886-1893.
- Walbert T., R.A. Harrison, D. Schiff, E.K. Avila, M. Chen, P. Kandula, J.W. Woo Lee, E. Le Rhun, G.H.J. Stevens, M. A. Vogelbaum, W. Wick, M. Weller, P. Y. Wen, E. R. Gerstner, SNO and EANO practice guideline update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro-oncology Vol 23 Issue 11 Pg 1835-1844, 2021. https://doi.org/10.1093/neuonc/noab152

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Prophylactic ASM

- There is little argument about using ASMs once a seizure has occurred and future seizures are predictable
- Our focus here is on prevention of the first seizure

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Prophylactic ASM

- Why prevent an initial seizure?:

  - it may occur at a time during the course of the disease process when it will constitute a severe hazard to the patient

  - permanent structural changes forming an epileptic focus may result from repetitive stimulation (kindling), preventing early seizures may reduce the risk of establishing a seizure focus

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Prophylactic ASM

- It has been reported that seizure frequency is inversely related to the degree of malignancy
  - oligodendrogliomas (WHO II) 81%
  - astrocytomas 66%
  - ependymomas 50%
  - GBM 42%
  - IDH1/2 mut increased sz

Lund, M. Epilepsy in association with intracranial tumours. Acta Psychiatr. Neurol. Scand. Suppl. 8:1-149, 1952

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Perioperative Use of ASM

- **A Prospective Randomized Trial of Perioperative Seizure Prophylaxis in Patients with Intraparenchymal Brain Tumors.**
- **Wu AS et al *J Neurosurg* 2013;118:873–83**
- **METHODS: Patients with brain tumors (metastases or gliomas) who did not have seizures and who were undergoing craniotomy for tumor resection were randomized to receive either phenytoin for 7 days after tumor resection (prophylaxis group) or no seizure prophylaxis (observation group).**

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Perioperative Use of ASM

- **RESULTS: The trial was closed before completion of accrual because Bayesian predictive probability analyses performed by an independent data monitoring committee indicated a probability of 0.003 that at the end of the study prophylaxis would prove superior to observation and a probability of 0.997 that there would be insufficient evidence at the end of the trial to choose either arm as superior.**
- **The incidence of all seizures was 18% in the observation group and 24% in the prophylaxis group ($p = 0.51$).**
- **Importantly, the incidence of early seizures (< 30 days after surgery) was 8% in the observation group compared with 10% in the prophylaxis group ($p = 1.0$).**
- **The prophylaxis group experienced significantly more adverse events (18% vs 0%, $p < 0.01$).**

- **Walbert T., R.A. Harrison, D. Schiff, E.K. Avila, M. Chen, P. Kandula, J.W. Woo Lee, E. Le Rhun, G.H.J. Stevens, M. A. Vogelbaum, W. Wick, M. Weller, P. Y. Wen, E. R. Gerstner, SNO and EANO practice guideline update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro-oncology Vol 23 Issue 11 Pg 1835-1844, 2021. https://doi.org/10.1093/neuonc/noab152**

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Drug delivery to the CNS: ASMs and chemotherapy affected

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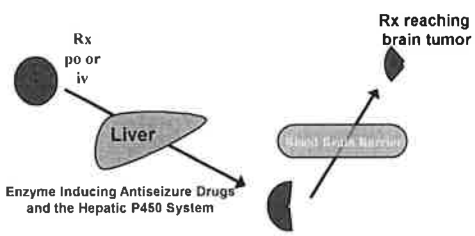
How much drug gets there?



NWOOA 2025 Courtesy Skip Grossman

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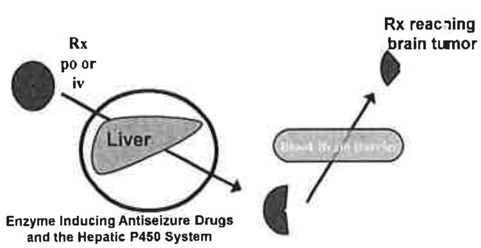
How much drug gets there?



Courtesy Skip Grossman

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Drug Metabolism

- **Major route : <u>liver</u>**
- **Many meds affect the metabolism of chemotherapy drugs by the liver**
  - **Faster – i.e., meds that induce liver enzymes. Example: phenytoin (Dilantin™)**
  - **Slower – valproic acid (Depakote™); large quantities of grapefruit juice**
  - **Not at all – levatirectam (Keppra™)**

Anticonvulsants can have major impact on chemotherapy metabolism

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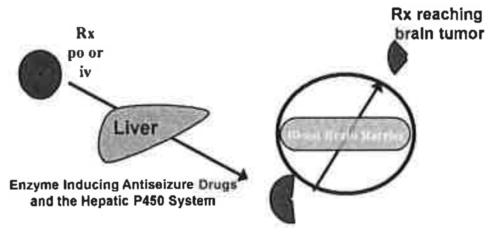
How much drug gets there?



Courtesy Stdp Grossman

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Antiseizure Medications

Group A

Anticonvulsants That Induce Hepatic Enzymes

Generic Name	Trade Name
Phenytoin	Dilantin
Carbamazepine	Tegretol
Phenobarbital	Phenobarbital
Primidone	Mysoline
Oxcarbazepine (1999)	Trileptal

Group B

Anticonvulsants That Cause Minimal or No Hepatic Induction

Generic Name	Trade Name
Valproic acid	Depakote
Gabapentin (1993)	Neurontin
Felbamate(1993)	Felbatol
Lamotrigine (1994)	Lamictal
Topiramate(1996)	Topamax
Tiagabine (1997)	Gabitril
Levetiracetam (1999)	Keppra
Zonisamide(2000)	Zonegran
Pregabalin(2005)	Lyrica
Lacosamide (2008)	Vimpat

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Recommendations

- In patients with newly dx brain tumors, antiseizure medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic anticonvulsants should not be used routinely in patients with newly diagnosed brain tumors

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Recommendation II

- In patients with brain tumors who have not had a seizure, tapering and discontinuing ASM after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing side effects

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Summary Cont'd

- AAN/SNO/EANO do not recommend ASM prophylaxis for newly dx brain tumor patients
- Think of brain tumors as a chronic disease
- Minimize drug interaction by selecting the ASM best for your patient when they are required

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Question

A newly diagnosed Glioblastoma patient comes to see you in Neurology Clinic post op day 7. She has never had a seizure and is on levitiracetam 500mg bid and dexamethasone 4mg bid. You would recommend all of the following EXCEPT: (which is false)

1) Wean the dexamethasone to off if tolerated -T
2) Wean off the levetiracetam -T
3) When the dexamethasone is taken twice a day, you recommend breakfast and lunch -T
4) Tell her she will be on levitiracetam life long -F

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Answer # 4

- **Recommend weaning the ASM 7-10 days post op.**

- *M.J.Glantz, B.F. Cole, P.A. Forsyth, L.D. Recht, P.Y. Wen, M.C. Chamberlain, S.A. Grossman, and J.G. Cairncross. Neurology. 2000; 54:1886-1893*
- *Walbert T., R.A. Harrison, D. Schiff, E.K. Avila, M. Chen, P. Kandula, J.W. Woo Lee, E. Le Rhun, G.H.J. Stevens, M. A. Vogelbaum, W. Wick, M. Weller, P. Y. Wen, E. R. Gerstner, SNO and EANO practice guideline update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro-oncology Vol 23 Issue 11 Pg 1835-1844, 2021. https://doi.org/10.1093/neuonc/noab152*

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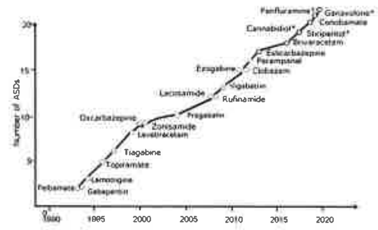
DEVELOPMENT OF ASMs

ASM approved by FDA since 1990



* Condition specific epilepsy

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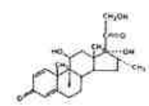
Dexamethasone



Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder

Cortisone, 25
Hydrocortisone, 20
Prednisolone, 5
Prednisone, 5
Dexamethasone, 0.75
Methylprednisolone, 4

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Dexamethasone

- **Dexamethasone is most often utilized for symptomatic and first-line treatment of brain tumor for several reasons, including the fact that it is the most potent steroid, has the best CNS penetration, the least mineralocorticoid side effects, the least protein-bound steroid and has a long biologic half-life (24–36 h):** Norden AD, Wen PY, Kesari S. Brain metastases. *Curr. Opin. Neurol.* 18(6),279–292 (2005).

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Steroid Interactions

- Decadron is a CYP3A4 inducer- meaning it affects how drugs are broken down in the liver (i.e.: could affect other drugs patients take- like seizure medication or chemotherapy)

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Dexamethasone 4mg Q 6 Stamp

- Dr. French in the early 1960s selected dexamethasone at 16mg a day (4mg Q 6 hours)- still in practice today
- "Don't think, you will only weaken the team", and "fly the mission as directed"- Asa Wilbourn MD, CCF

- Let's actually think about what makes sense
- If the ½ life is >24 hrs., why are we giving it 4 times a day?

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Dexamethasone Dosing

- Randomized study of 4, 8 and 16 mg/day dosing of dexamethasone
- Found no advantage to higher dosing in patients who were not felt to be in impending danger of cerebral herniation
- Dexamethasone dosage of 8 mg/day (Group 1) was compared to 16 mg/day (Group 2), followed by a comparison of 4 mg/day (Group 3) versus 16 mg/day (Group 4).
- Both groups showed an improvement, there was no significant difference in KPS improvement comparing the 8-mg group versus the 16-mg group at day 7
- In the second trial, again both groups showed improvement. However, no significant difference between the 4- and 16-mg group
- Side effects (Cushingoid changes and extremity edema) occurred more frequently in the 16 mg/day versus the 4 mg/day group at Day 28
- Vechi CJ et al (1994) Dose-effect relationship of dexamethasone on Karnofsky performance in metastatic brain tumors: a randomized study of doses of 4, 8, and 16 mg per day. Neurology 44(4) 675–680

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Steroid Side Effects (Dose and Time Dependent)

- Acne
- Insomnia
- Vertigo
- Increased appetite
- Weight gain
- Impaired skin healing
- Depression
- Euphoria
- Hypertension (high blood pressure)
- Increased risk of infection
- Raised intraocular pressure
- Vomiting
- Dyspepsia
- Confusion
- Irritability
- Nausea
- Malaise
- Headaches
- Cataract
- Adrenal suppression
- Growth stunting (in children)
- Cushing's syndrome
- Peptic ulcer
- Osteoporosis (brittle bones)
- Myopathy
- Diabetes mellitus type 2
- Hyperglycaemia (high blood sugar)
- Pancreatitis (swelling of the pancreas)
- Sodium and water retention
- Mania
- Psychosis
- Glaucoma
- Cardiomyopathy
- Abdominal distention
- Corneal or scleral thinning
- Candidiasis (thrush)
- Skin atrophy
- Bruising
- Telangiectasia
- Striae

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Steroids Summary

- Dexamethasone is the steroid of choice for brain tumor patients to tx edema
- Constant re-evaluation
- Recommend H2 blocker (decrease GI risks?)
- AM loading (long ½ life)
- Look for thrush

- Think bone health- Ca/VitD for long term use
- PJP prophylaxis (pentamidine/Bactrim) if extended use
- Can use Bevacizumab to wean steroids
- ? Boswellia to help decrease edema- inhibits 5 Lipoxygenase (LO)

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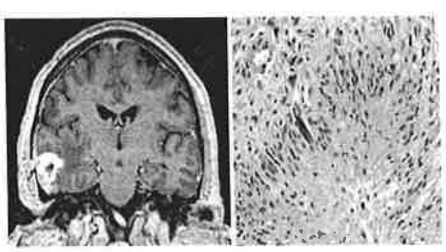
Glioblastoma (GBM) (no more multiforme)



MLE or 12-15-20mths from dx

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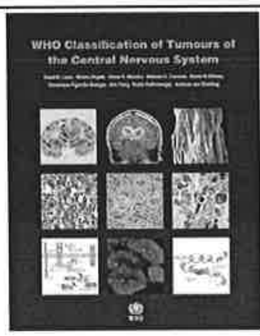

2016

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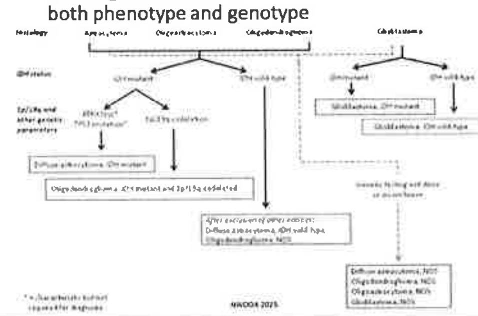
Nosological shift to a classification based on both phenotype and genotype



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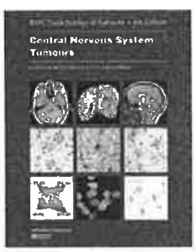
WHO CLASSIFICATION OF TUMORS: 2021



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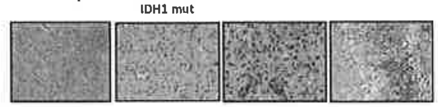
Genetics of Malignant Astrocytomas

S
e
c
o
n
d
a
r
y

-17p/Δp53
+PDGFα →
-22q

-13q/ ΔRb
-19q
-7p/-7q
+MDM2
IDH1 mut

→ +PDGFα receptor
+PDGFA
-10-, -10q ⟶



Normal | LGA (WHO 2 not II) | (WHO 3 not III) No longer anaplastic | GBM (WHO 4 not IV)- IDH1 wt

D
e
N
o
v
o

+EGFR
-10p, -10q ⟶ + VEGF
EGFRviii

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Courtesy Dr Barnett and modified

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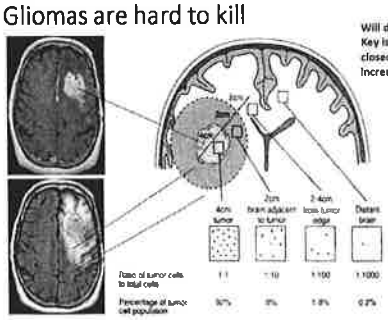
Gliomas are hard to kill

Will discuss Focused Ultrasound later: Key is treating the flair signal, the supposed closed (intact) barrier- can we increase penetration of chemotherapy?



Courtesy Dr Vogelbaum

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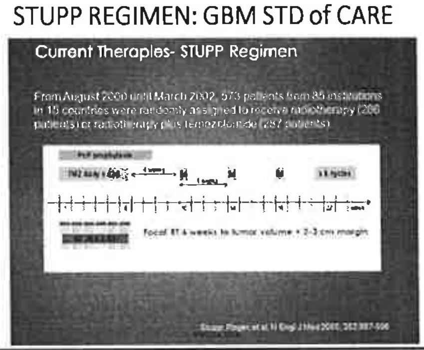
STUPP REGIMEN: GBM STD of CARE



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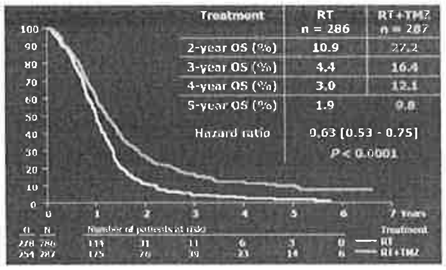
Stupp Protocol: Update



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Question

A 60 year old female with an unremarkable past medical history presents with progressive headaches. Imaging studies show a large right frontal mass which on gross total resection shows a Glioblastoma (GBM). Initial standard of care for this patient is which of the following?

1) **Radiation therapy alone**
2) **Chemotherapy alone**
3) **Combined radiation and chemotherapy**
4) **Hospice**

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Answer # 3

- **The current initial standard of care for newly diagnosed glioblastoma patients age 18-70 years is the combination of radiation and chemotherapy (Temodar) on the Stupp Regimen.**

- *Roger Stupp et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma N Engl J Med 2005; 352:987-996*

- **Trick question?**
- **NCCN Guidelines rec evaluating all GBM patients for clinical trials**

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Astrocytoma Drug Resistance to Temozolomide: MGMT

O6-Methylguanine-DNA Methyltransferase

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MGMT

- **DNA repair enzyme in tumors**
- **Repairs DNA that has been methylated by alkylating agents (e.g., temozolomide or BCNU, CCNU)**
- **When the MGMT gene is methlyated, no MGMT is produced (gene silencing)- this is better for the patients; unmethylated worse prog**
- **Therefore, when present and active, cells are resistant to these drugs**

MGMT = O6-Methylguanine-DNA Methyltransferase
MGMT = O6-Methylguanine-DNA Methyltransferase
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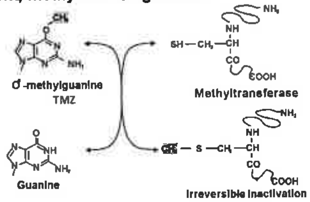
O6-Methylguanine-DNA Methyltransferase (MGMT)

TMZ, alkylating agent, methylates O6-guanine

MGMT

- DNA Repair enzyme
- Removes alkyl-groups from O6alkylguanine
- Linked with resistance to alkylating agent therapy (TMZ)



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MGMT and Survival

- From EORTC 26981 Trial: The MGMT promotor was methylated in 45% of 206 tumors. A clear survival benefit was noted among patients whose tumors contained a methylated MGMT promotor (ie decreased resistance mechanism) treated w TMZ+XRT compared to radiotherapy alone (21.7 mths vs 15.3 mths).

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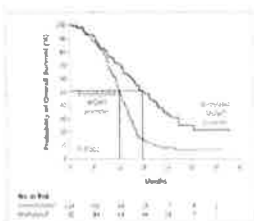
GBM Overall Survival according to Methylation of MGMT promoter



Hegi M. NEJM 352:997-1003, 2005

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What to do with MGMT unmethylated patients?

- Checkmate CA209-498: A Randomized Phase 3 Open Label Study of Nivolumab vs Temozolomide Each in Combination with Radiation Therapy in Newly Diagnosed Adult Subjects with Unmethylated MGMT (tumor 06-methylguanine DNA methylatransferase) Glioblastoma
- Hypothesis: Treatment with radiation therapy plus nivolumab (RT + Nivolumab) will improve overall survival (OS) compared with radiation therapy plus temozolomide (RT + TMZ) in subjects with newly diagnosed unmethylated MGMT GBM- unfortunately was a negative trial.

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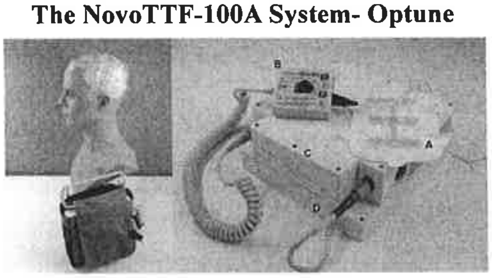
The NovoTTF-100A System- Optune



Fonkem E, Wong ET. Exp Rev Neurother 2012;12:895-899

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Tumor Treating Fields

- Use of electric fields as an anti-mitotic therapy for cancer patients
- Invented by: Dr. Yoram Palti, professor emeritus at the Technion in Israel
- Manufactured by Israeli company Novocure under the trade name Optune (formerly NovoTTF-100A)
- Approved by the U.S. Food and Drug Administration (FDA) in April 2011 for the treatment of patients with recurrent glioblastoma
- Optune was approved by the FDA for newly diagnosed glioblastoma on Oct. 5, 2015

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- NovoTTF Therapy mechanism of action
  - Antimitotic at end cell cycle

- Clinical trial data:
  - EF-07 pilot study; N=10; mOS 36mths
  - EF-11 phase III trial; randomized TTF vs Chemo post Stupp; OS sim but QOL increased TTF
  - PRIDe: All tx patients; Med OS 9.6mths

Phase III post Stupp TMZ vs TTF+TMZ- the TTF+TMZ gp mean OS ~ 20mths

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Conclusion

1. The NovoTTF-100A System shows comparable efficacy with cytotoxic chemotherapies in GBM patients
2. Patients treated with NovoTTF-100A experience lower toxicity than those treated with chemotherapies
3. When TTF are combined with TMZ post XRT/TMZ median OS is increased to ~ 20mths

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Douro Valley Portugal

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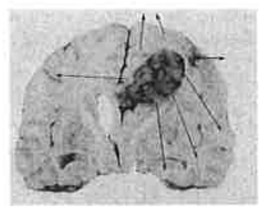
Oligodendroglioma



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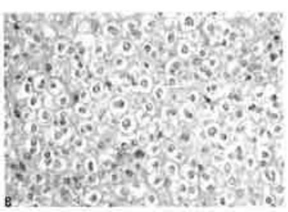
Oligodendroglioma



H&E: Classic "fried egg" LGO

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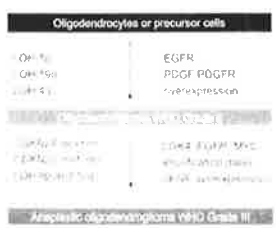
Oligodendrogliomas



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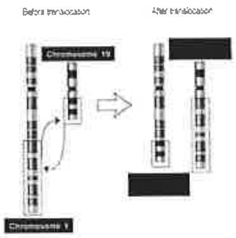
Oligodendroglioma: New WHO need t (1p;19q) and IDH1 mutation for classification

- **1p/19q codeletion caused by 1p 19q translocation t(1p;19q)**



1p/19q co-deletion = t(1p;19q)

Jenkins RB, Cancer Res. 66:9852-61, 2006

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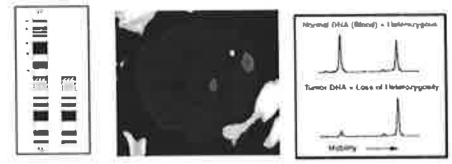
Chromosome 1p **FISH** **PCR**



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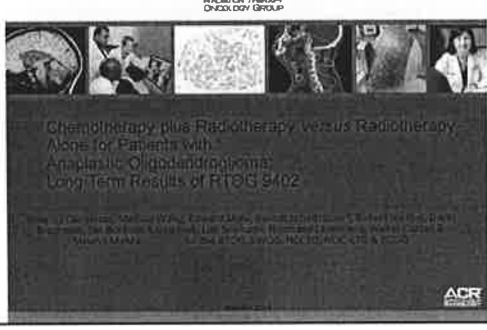
RTOG Radiation Therapy Oncology Group



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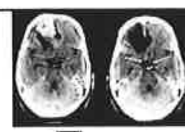

9402 Study Design
(pure & mixed histologies)

STRATIFY		RANDOMIZE	
	Age <50 *vs.* ≥ 50 KPS 60-70 *vs.* ≥80 Degree of anaplasia		Experimental Arm: Intensive-PCV x 4 (q 6 wks) then RT Standard Arm: RT

I-PCV = procarbazine, CCNU (lomustine) and vincristine ⟶ SURVIVAL

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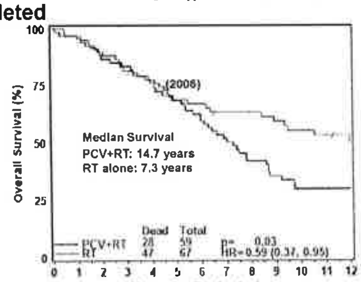
Overall Survival by R_X with 1p/19q co-deleted



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Conclusions from Long Term Results

- Patients with 1p/19q co-deleted tumors live significantly longer after PCV+RT
- Replacing PCV with TMZ?

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Oligodendroglioma Survival

- CCF experience with oligodendrogliomas
- N=96
- Prognosis related to allelic loss 1p and 19q
- Improved survival so longer time to deal with seizures-start thinking of brain tumor as a chronic disease

Kanner et al J Neurosurgery 2006;104:542-550

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Tanzania

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Angiogenesis in Tumor Growth

- Father of angiogenesis in tumor biology
- Seminal paper in NEJM described the "angiogenic process" (1971)
- Born in Cleveland

Judah Folkman (1933-2008)

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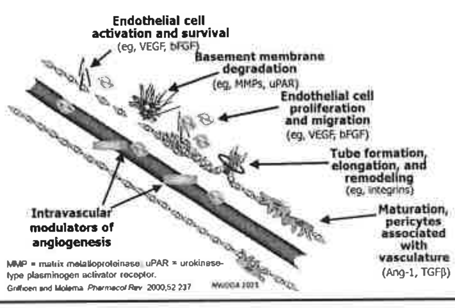
The Angiogenic Process



MMP = matrix metalloproteinase; uPAR = urokinase-type plasminogen activator receptor.

Griffioen and Molema. *Pharmacol Rev*. 2000;52:237

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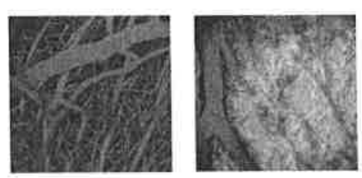
Abnormal vessels in GBM



Normal brain vessels　　Brain tumor vessels

Leaky
Poor circulation
Hypoxia
Angiogenesis

Jain RK et al Angiogenesis in brain tumours. Nat Rev Neurosci. 2007 Aug;8(8):610-22. Review

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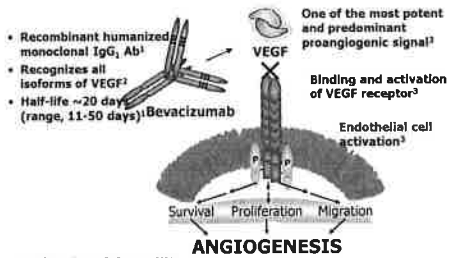
Bevacizumab Binds VEGF: A Key Mediator of Angiogenesis



1 Avastin® (bevacizumab) PI December 2004
2 Presta et al Cancer Res 1997 57 4593
3 Ferrara et al Nat Med 2003,9 669

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Bevacizumab (B) and CPT-11(C) in the Treatment of Relapsed Malignant Glioma*

- 21 pts (11 GBM, 10 other high grade gliomas)
- Median no of prior Rx: 3 (2–10)
- 6-wk cycle, B: 5 mg/kg, every other wk × 2, C: 125 mg/m^2 every wk × 4, 2 wk rest
- Overall RR ~ 43%
- 1 CR, 8 PRs, 11 SD

*Stark- Vance. World Federation of Neuro-Oncology Second Quadrennial Meeting and the Sixth Meeting of the European Association for Neuro-Oncology May 5–8, 2005, Edinburgh, United Kingdom

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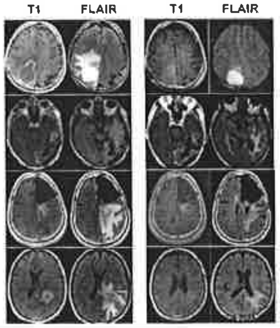

Axial gadolinium-enhanced T1-weighted and fluid-attenuated inversion-recovery (FLAIR) images of 4 selected patients (from top to bottom, Patients 1, 2, 3, and 5) with radiation necrosis obtained before and after bevacizumab treatment

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Adverse Events Associated With Bevacizumab

Serious adverse events

- GI perforation*
- Wound healing complications*
- Hemorrhage*
- Hypertensive crisis- PRES
- Nephrotic syndrome
- Arterial thromboembolic events

Most common adverse events of any severity

- Asthenia
- Pain
- Abdominal pain
- Hypertension
- Diarrhea
- Headache
- Nausea
- Vomiting
- Anorexia
- Stomatitis
- Constipation
- Epistaxis
- Dyspnea
- Exfoliative dermatitis
- Proteinuria
- Upper respiratory infection

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Bevacizumab: Upfront GBM Studies

- **2 RCT of upfront bevacizumab (Avastin) plus Stupp Regimen were completed. Both were negative trials for improving OS- not typically given upfront**

Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014; 370: 709- 722.

Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014; 370: 699- 708.

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Laser Interstitial Thermal Therapy - LITT

- Uses LASER scatter to heat brain
- Bare fiber optics
- 1994 – Kahn, Schwarzmaier et al.
- 1998 - Morrison, Jolesz et al.
- Limitations:
  - Char
  - Directionality
  - Heat conduction prediction / monitoring

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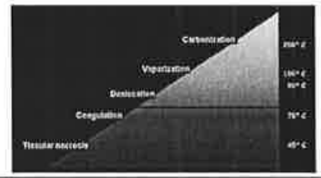
LITT - Background

- Heat kills cell
  - (43-55 °C) Apoptosis, necrosis
    - transmembrane proteins, melting lipid bilayer
  - (>57 °C) Coagulation



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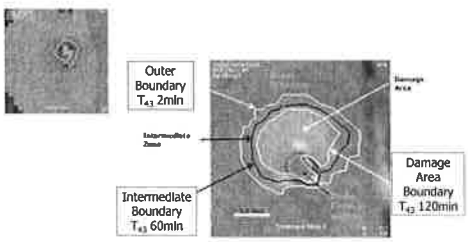
Real-Time Thermal Dosimetry Thermal Damage Threshold (TDT)



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AutoLITT & IMRIS Integration

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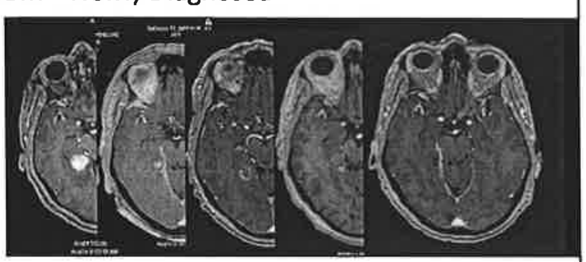
GBM – Newly Diagnosed



24 Hours 3 Mths 1 Year 24 Mths

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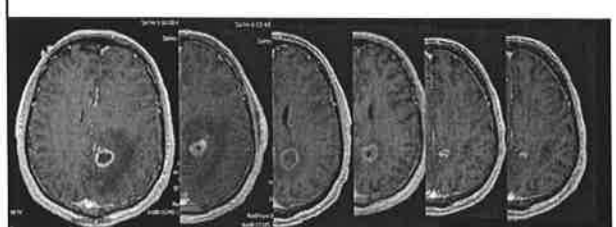
Cingulate GBM – Newly Dx'd



3 mths 7 mths 12 mths 14 mths

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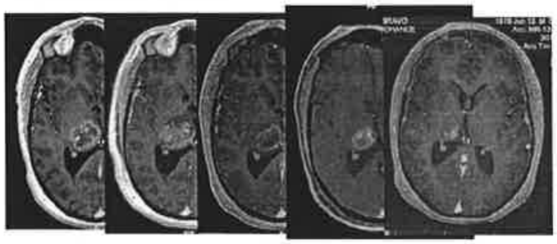
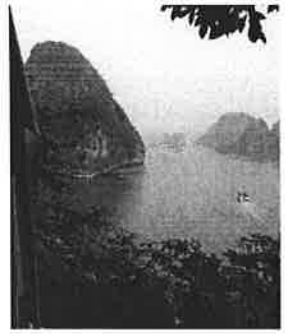
Thalamic GBM



Pre-op Post-op 3 Mths 6 Mths 9 Mths

91



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Ultrasound (US)

- Ultrasonic waves are sound waves that propagate through matter w frequencies typically above 20,000Hz
- Ultrasound was used for submarine detection in WWI
- High Intensity Focused Ultrasound (HIFU) for intracerebral ablation was pioneered by the Fry brothers
- Used 4 piezoelectrode transducers to pinpoint lesions
- HIFU originally guided by US but limited guidance accuracy and real-time temperature monitoring
- Intraop MRI could use magnetic resonance guided focused ultrasound (MRgFUS): real-time image acquisition of target; can measure sonication temperature; determine ablated volume by T2-weighted fast spin echo sequences

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Ultrasound: Principles

- During MRgFUS a small target is heated w US rays, a technique called sonication
- Tx at an intensity of 100-10,000 Watt/cm² to max energy accumulation and cause coagulation necrosis
- For intracranial tx, a piezoelectrode transducer converges US energy (1-3 MHz) to target tissue
- A temperature of >56 °C for 2 sec or more leads to coagulative necrosis
- Result is cell death

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MRgHiFU Applications

- Functional NSG: target thalamus, subthalamus or Basal Ganglia for treatment of neuropathic pain, Parkinson's Disease and essential tremor (2016 FDA Approval)
- CNS neoplasms: GBM- ongoing trials

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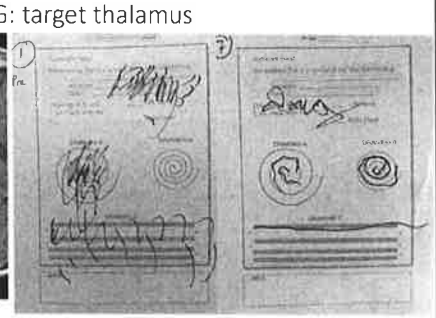
Functional NSG: target thalamus



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Low Intensity Focused Ultrasound (LiFU): Opening the Blood Brain Barrier (BBB)

- MRgFUS is used to non-invasively open the blood brain barrier
- Utilize 1024 individual transducer elements around skull w real-time image guidance
- LiFU delivers <1% of energy required for thermal ablation by interacting w IV injected microbubbles (Definity™) to create a temporary opening of the BBB
- Due to low energy the volume of BBB opening can be expanded and customized for shape and location (on the trial completed ~ 110cc vol)
- Animal studies: barrier is open ~ 8 hrs. w/o axonal or neuronal injury

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Definity™

- Oscillation of the microbubbles causes mechanical effects on the capillaries in the target area, resulting in a transient loosening of the blood-brain barrier (penetrable gaps in tight endothelial junctions). (Interest in developing FUS specific microbubble)

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Frame Placement

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Frame Placement

Haircut

Frame is placed low

Shave

Bladder will fill w water For cooling

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Real-Time Monitoring

Transducer in place

Need excellent Neuro-radiology staff and technicians

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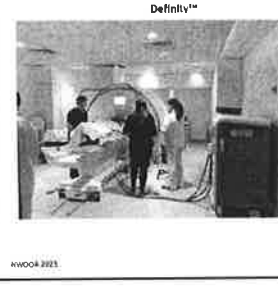
Treatment is Completed in MRI

Definity™



Water Bath

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Case Planning

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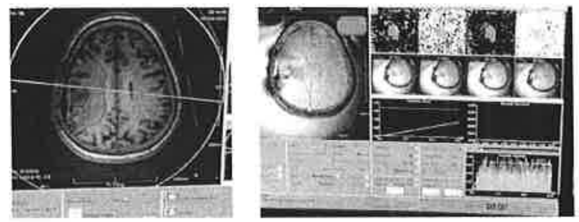
Defined treatment area and sonication



Vol target tx: max 110 cc

Sonication

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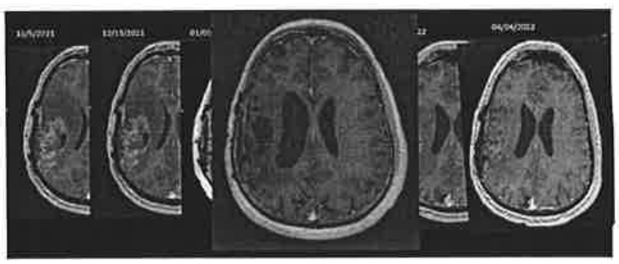
Patient X: s/p 6 cycles BBBO and IV carboplatin



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Symptom Management

Work with a multidisciplinary team- ounce of prevention

Allows discussion of clinical trial options

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Setting the Stage

- Most randomized controlled trials (RCTs) performed in glioma patients indicate that new treatments do not improve overall survival, they have shown to prolong the period of progression-free survival. Chinot OL, et al. AVAglio: Phase 3 trial of bevacizumab plus temozolomide and radiotherapy in newly diagnosed glioblastoma multiforme. Adv Ther. 2011;28(4):334–340.
- It is crucial that patient level of functioning and well-being is maintained during that progression-free period.
- Maintenance or improvement of health-related quality of life (HRQoL) is one of the main treatment goals in this patient group
- Both treatment and disease progression may cause a further deterioration in HRQoL.
- 5539 patients from prev. published phase II and III RCT with at least baseline HRQoL scores had a median time from randomization to progression of 7.6 months. Coomans MB, et al Factors associated with health-related quality of life (HRQoL) deterioration in glioma patients during the progression-free survival period. Neuro Oncol. 2022 Dec 1;24(12):2159-2169. doi: 10.1093/neuonc/noac097. PMID: 35404443; PMCID: PMC9713503. UCNS MOC Paper 2023
- Almost half of the included patients experienced a deterioration in HRQoL during their progression-free survival time.
- We have to do a better job of maintaining HRQol (how to determine disease progression?)

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Supportive Care

- Goal of supportive care in glioma patients: to improve the QOL of patients and caregivers and reduce symptom burden
- Really talking about Palliative care (PC) whose goal is not primarily aimed at prolongation of life or cure. Koekkoek et al. Palliative care and end-of-life care in adults with malignant brain tumors. Neuro-oncology 25(3), 447-456 2023. UCNS MOC Paper 2024
- Some data in lung cancer patients that PC can affect length of survival. Temel JS, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. The New England journal of medicine 2010; 363(8): 733-42.
- Looking at patients physical, cognitive, mood, social and spiritual needs
- The World Health Organization (WHO) states that PC is applicable early in the course of illness and only 14% who require it, receive it
- PC involvement may not only improve symptom management and caregiver satisfaction but also reduce health costs Zimmermann C, et al Effectiveness of specialized palliative care: a systematic review. Jama 2008; 299(14): 1698-709.

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Supportive Care

- NCCN Guidelines for patients: Gliomas: nice resource for patients
- www.nccn.org/patients/guidelines/content/PDF/brain-gliomas-patient.pdf
- Updated Cancer-Related Fatigue, version 2.2024- published Oct 20 2023
- Look for brain tumor or cancer support groups for patients- if you do not have one, consider the American Brain Tumor Association (ABTA). Maliya S, Daniels M, Kanter C, et al. A qualitative analysis of the benefits and barriers of support groups for patients with brain tumors and their caregivers. Support Care Cancer. 2020;28(6):2659-2667. doi:10.1007/s00520-019-05069-5
- ABTA offers supportive CareLine staff, Patient & Caregiver Mentor Support, and an online support community.

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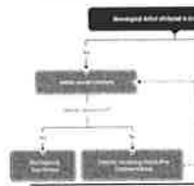
Supportive Care

- EANO-ESMO Clinical Practice Guideline for Brain Tumors: Steroids
- Neurological and vascular complications of primary and secondary brain tumors: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up Roth et al Annals of Oncology Vol 32 Issue 2, P171-182, 2021: DOI:https://doi.org/10.1016/j.annonc.2020.11.003



Evidence linking steroid use to inferior survival in glioblastoma: Pitter K.L et al l al. Corticosteroids compromise survival in glioblastoma. Brain. 2016; 139: 1458-1471

Immunotherapy approaches for primary and metastatic brain tumors in which steroid use may be detrimental. Okada H. et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. Lancet Oncol. 2015; 16: e534-e542

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Boswellia serrata (BS)

44 patients with primary or secondary malignant cerebral tumors were randomly assigned to radiotherapy plus either BS 4200 mg/day or placebo

Reduction of cerebral edema of >75% was found in 60% of patients receiving BS and in 26% of patients receiving placebo (P = .023)

BS did not have a significant impact on quality of life or cognitive function

Kirste S, et al Boswellia serrata acts on cerebral edema in patients irradiated for brain tumors: a prospective, randomized, placebo-controlled, double-blind pilot trial. Cancer. 2011 Aug 15;117(16):3788-95. doi: 10.1002/cncr.25945. Epub 2011 Feb 1. PMID: 21287538.

Dr Chao uses GNC Boswellia extract 450mg 3 tabs tid (Personal Communication)

Group at Swedish were using Boswin Gold 4000 mg daily (Personal Communication)

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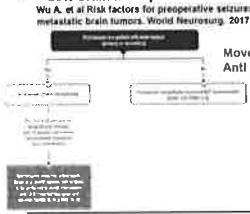
Supportive Care

- EANO-ESMO Clinical Practice Guideline for Brain Tumors: Seizures
- Lifetime risk for sz with diffuse glioma exceeds 50% with possible link to IDH1 mutations Chen H et al. Mutant IDH1 and seizures in patients with glioma. Neurology. 2017; 88: 1805-1813
- ~ 20% brain mets present with sz and tumor control is best predictor of outcome. Wu A. et al Risk factors for preoperative seizures and loss of seizure control in patients undergoing surgery for metastatic brain tumors. World Neurosurg. 2017; 104: 120-128



Moved away from using the term anti epileptic drug (AED) to Anti seizure medication (ASM)

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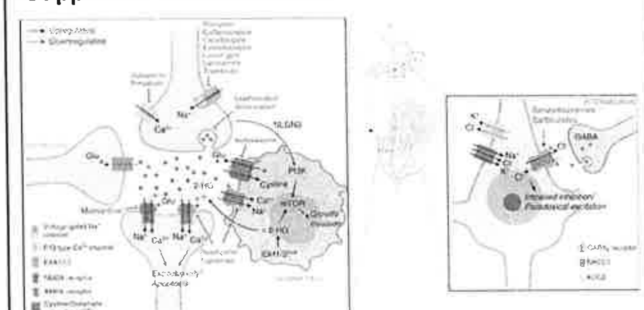
Supportive Care: Seizures



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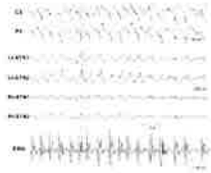
Electroencephalogram (EEG)

If uncertain if patients' "event" is a seizure, consider an EEG

Can be routine (20 min), prolonged (2 hours) or can consider ambulatory EEG 24-72 hrs., or in-patient video EEG monitoring



Recordings of a clonic seizure of the right arm. EEG: C3 and P3 placed according to the International 10/20 System. Lt-STN1 and Lt-STN2: (depth electrode). EMG: bipolar recording of the right biceps muscle. Note the polyspike±wave pattern in the cortical EEG.

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Anti-seizure Medication (ASM): Practice Parameter from the AAN, SNO and EANO

- Anticonvulsant prophylaxis in patients with newly diagnosed brain tumor. Report of the Quality Standards Subcommittee of the American Academy of Neurology. M.J.Glantz, B.F. Cole, P.A. Forsyth, L.D. Recht, P.Y. Wen, M.C. Chamberlain, S.A. Grossman, and J.G. Cairncross. Neurology. 2000; 54:1886-1893.
- Walbert T., R.A. Harrison, D. Schiff, E.K. Avila, M. Chen, P. Kandula, J.W. Woo Lee, E. Le Rhun, G.H.J. Stevens, M. A. Vogelbaum, W. Wick, M. Weller, P. Y. Wen, E. R. Gerstner, SNO and EANO practice guideline update: Anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Neuro-oncology Vol 23 Issue 11 Pg 1835-1844, 2021. https://doi.org/10.1093/neuonc/noab152
- No Class I evidence for the routine use of ASM in newly dx brain tumor patients that have never had a seizure

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End Of Life and ASM Use

May have impaired consciousness, swallowing difficulties

Intranasal midazolam and rectal diazepam have shown similar efficacy in the acute treatment of seizures in non tumor patients Holsti M. et al. Intranasal midazolam vs rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy. Archives of pediatrics & adolescent medicine 2010; 164(8): 747-53

Prospective study among 25 glioma patients, intranasal midazolam appeared to be a feasible way to treat acute seizures Koekkoek JA, et al. Antiepileptic drug treatment in the end of-life phase of glioma patients: a feasibility study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2016; 24(4): 1633-8

Options include: Subcutaneous midazolam, subcutaneous levetiracetam (unlicensed 100mg/ml), and subcutaneous phenobarbital are suitable alternatives to oral treatment. Intramuscular phenobarbital in patients assisted at home can be an option.

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Discuss ASM Precautions

Discuss driving and other sz related limitations

For patients on ASM discuss mood at each visit: FDA in 2008 came out and reported an increased risk of suicide thought or behavior for patients on ASM so ask

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Ha Long Bay NE Vietnam

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Supportive Care

- EANO-ESMO Clinical Practice Guideline for Brain Tumors: Neurocognitive Impairment
- Memory and executive functioning are the most frequently impaired domains. Wefel J.S. et al Neurocognitive functioning and genetic variation in patients with primary brain tumors. Lancet Oncol. 2016; 17: e97-e108
- Validated neuropsychological tests: Hopkins verbal learning test for verbal memory, Rey–Osterrieth complex figure test (visuoconstruction, visual memory), controlled oral word association test (verbal fluency), Stroop test (interference, executive functioning) and the trail making test (attention, executive functioning)
- Prevention is helpful: awake craniotomy or mapping of eloquent brain functions may preserve cognitive and neurological integrity, Limited dose per fraction and lower overall radiation dose, focal RT instead of whole brain radiotherapy (WBRT) and hippocampal sparing during WBRT. Adding Memantine may decrease neurocog decline
- Difficult to generalize use of methylphenidate, dexamphetamine or donepezil
- Phase II trial of newly dx GBM patients, proton therapy vs IMRT did not prevent cog failure at 48 mths. Brown et al. A prospective phase II randomized trial of proton radiotherapy vs IMRT for patients with newly diagnosed GBM. Neuro-onc 2021 23(8):1337-1347.
- Cognitive Rehab may offer benefits. Gehring K et al Cognitive rehabilitation in patients with gliomas: a randomized, controlled trial. J Clin Oncol. 2009; 27: 3712-3722

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Supportive Care

- EANO-ESMO Clinical Practice Guideline for Brain Tumors: Venous Thromboembolism and Stroke
- Venous thromboembolism (VTE) is increased in cancer patients, with a particularly high risk in brain tumor patients. Petterson T.M. et al. Risk of site-specific cancer in incident venous thromboembolism: a population-based study. Thromb Res. 2015; 135: 472-478
- Recurrent VTE may be observed in a third (27%) of glioblastoma patients Edwin N.C. et al. Recurrent venous thromboembolism in glioblastoma. Thromb Res. 2016; 137: 184-188

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Supportive Care

- EANO-ESMO Clinical Practice Guideline for Brain Tumors: Venous Thromboembolism and Stroke
- Once the diagnosis of VTE has been confirmed, anticoagulation should start immediately. Parenteral anticoagulants (e.g. LMWH) are recommended for treatment and secondary prevention of VTE in patients with active cancer for 3-6 months, including those with brain tumors. Ay C. et al. Antithrombotic therapy for prophylaxis and treatment of venous thromboembolism in patients with cancer: review of the literature on current practice and emerging options. ESMO Open. 2017; 2: e000188
- In glioblastoma patients, an incidence of intracranial hemorrhage of 3%-5% has been reported under prophylactic LMWH. Perry J.R. et al. PRODIGE: a randomized placebo-controlled trial of dalteparin low-molecular-weight heparin thromboprophylaxis in patients with newly diagnosed malignant glioma. J Thromb Haemost. 2010; 8: 1959-1965
- Risk of intracranial hemorrhage for patients with brain metastases treated with therapeutic anticoagulation is probably not increased. Hunter B.D. et al. anticoagulation for the treatment of venous thromboembolism in patients with brain metastases: a meta-analysis and systematic review. J Thromb Thrombolysis. 2017; 44: 392-398

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Supportive Care

- EANO-ESMO Clinical Practice Guideline for Brain Tumors: Venous Thromboembolism and Stroke
- In glioma patients, strokes are not associated with the WHO grade and do not differ between histological subtypes. Seidel C. et al. A comprehensive analysis of vascular complications in 3,889 glioma patients from the German Glioma Network. J Neurol. 2013; 260: 847-855
- Primary brain tumor patients, the main causes of ischemic stroke include the late consequence of RT and hypercoagulable states. Seidel C. et al. A comprehensive analysis of vascular complications in 3,889 glioma patients from the German Glioma Network. J Neurol. 2013; 260: 847-855
- Bevacizumab may moderately increase the risk of stroke.
- No specific data are available on brain metastasis patients.
- Thrombolytic agents such as recombinant tissue plasminogen activator in patients with malignant brain tumors is generally recommended. Antiplatelet drugs should be considered for secondary prophylaxis as in the general ischemic stroke patient population.
- Other vascular complications include thrombotic microangiopathy, posterior reversible leukoencephalopathy syndrome, radiation-induced vasculopathy including stroke-like migraine attacks after RT (SMART) syndrome, Moya Moya-like vasculopathy and microbleeds.

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Supportive Care: Fatigue

- Cancer related fatigue not well understood but common in brain tumor patients affecting up to 90% of malignant glioma patients at some point
- MOA: thought to involve increased blood levels of inflammatory cytokines influencing neuroendocrine function and decreased levels of glutamine and tryptophan
- Management: Pharmacologic or non pharmacologic (physical exercise or cognitive behavioral therapies)
- No evidence suggesting a significant benefit from modafinil, armodafinil, methylphenidate or donepezil for the treatment of fatigue in stable brain tumor patients after treatment
- Cochrane review did not find strong evidence to support any pharmacological or non-pharmacological treatment for fatigue in patients with brain tumors Day J. et al. Interventions for the management of fatigue in adults with a primary brain tumor. The Cochrane database of systematic reviews 2016; 4: Cd011376.

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Supportive Care/Symptom Management: Fatigue

- NCCN Patient Guidelines: recommend yoga, Cognitive behavioral therapy (CBT) using cognitive restructuring to notice stress-producing or other negative thoughts, using mindfulness (practice of paying attention in the current moment), acupuncture, massage, CBT for sleep hygiene, bright white light therapy, seeing nutritionist, medication review
- American Ginseng? Mayo study in 2013: decreased cancer related fatigue with 2,000mg a day of pure ground American Ginseng. Barton D. L., et al (2013).Wisconsin Ginseng (Panax quinquefolius) to improve cancer-related fatigue: A randomized, double-blind trial, N07C2. Journal of the National Cancer Institute, 105(16), 1230–1238. 10.1093/jnci/djt181
- Lemke EA. Ginseng for the Management of Cancer-Related Fatigue: An Integrative Review. J Adv Pract Oncol. 2021 May;12(4):406-414. doi: 10.6004/jadpro.2021.12.4.5. Epub 2021 May 1. PMID: 34123477; PMCID: PMC8163251.

- Exercise may also improve cognitive function and fatigue. 34 WHO grades II/III glioma randomized to a home-based remotely coached exercise group or an active control group. Exercised 3 times per week for 20-45 minutes, with moderate to vigorous intensity, during 6 months. Gehring K, et al A pilot randomized controlled trial of exercise to improve cognitive performance in patients with stable glioma: a proof of concept. Neuro Oncol. 2020 Jan 11;22(1):103-115. doi: 10.1093/neuonc/noz178. PMID: 31755917; PMCID: PMC6954415.

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Summary

- Image patient 24-48 hours post op
- AAN/SNO/EANO do not rec routine long term ASM prophylaxis
- Steroids should have am loading and constant reevaluation
- Consider trials for GBM patients
- Std care for GBM is XRT+TMZ on Stupp Regimen +\-TTF
- 1p19q co-deletion is prognostic marker and defines oligodendrogliomas
- IDH1 is prognostic marker
- MGMT methylation is treatment marker
- Bevacizumab decreases brain edema but tumor affect? Upfront trials negative for OS
- Laser interstitial thermal therapy (Neuroblate) puts another tool in the belt
- FUS to open the BBB may provide a new way of getting drugs into the CNS
- For GBM always think clinical trials

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Symptom Management: Conclusions

Work with a multidisciplinary team- ounce of prevention

Gliomas are infiltrating tumors so broad spectrum of symptoms are possible

Consider Palliative Care and support groups for your patients

Steroid use should be constantly evaluated for need, side effects and dosing; not everyone needs the "neurosurgical stamp"; role for Boswellia?

Antiseizure medication prophylaxis is not recommended for newly dx tumor patients. Wide variety of medication options. Discuss sz precautions

Neurocognitive problems and fatigue are common: consider Neuropsych testing; CBT, Exercise, role for American Ginseng?

Venous thromboembolism (VTE) is increased in cancer patients- follow tx algorithms

Strokes are often related to late radiation side effects (bevacizumab increased risk). Risk of potential bleeding on anticoagulation must be considered

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A Team Approach to
Individualized Care

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