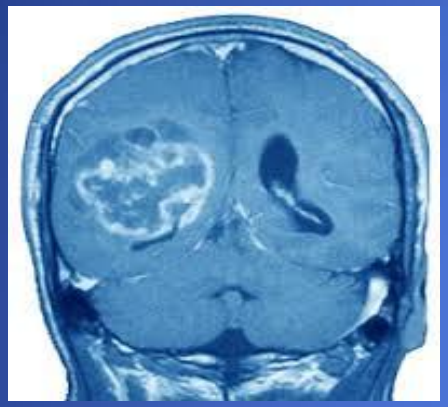
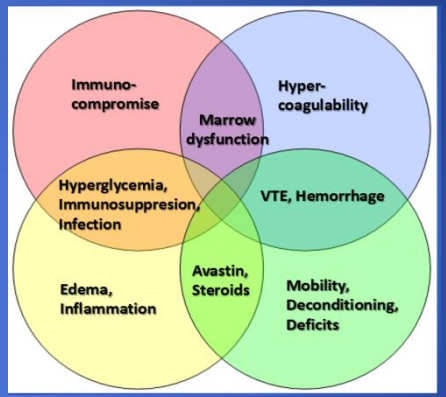
Evidenced-Based Symptom-Directed Treatments in Neuro-Oncology





Erin M. Dunbar, MD

Director, Neuro-Oncology, Piedmont Brain Tumor Center

Member, MD Anderson Provider Network

Palliative & Hospice Medicine, Medical-Oncology, PAH, Atlanta, GA

erin.dunbar@piedmont.org

Cell: 1-404-858-7317

No Relevant Disclosures

Erin M. Dunbar, MD

Director, Neuro-Oncology Program, Piedmont Brain Tumor Center

Member, MD Anderson Cancer Center Network

Palliative & Hospice Medicine, Oncology, PAH, Atlanta, GA

Erin.dunbar@piedmont.org

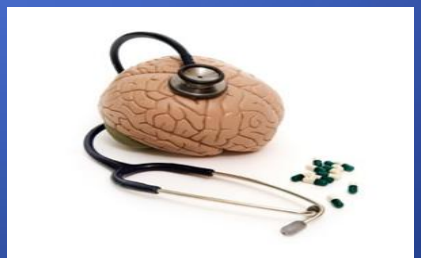
Cell: 1-404-858-7317

Piedmont

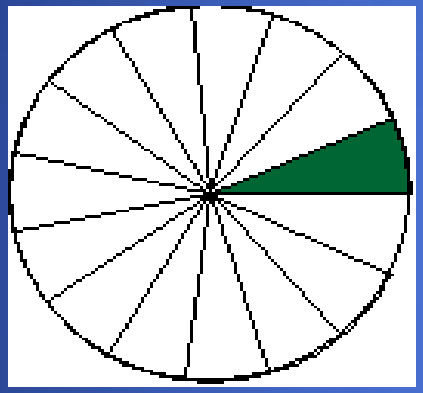
Brain Tumor Center

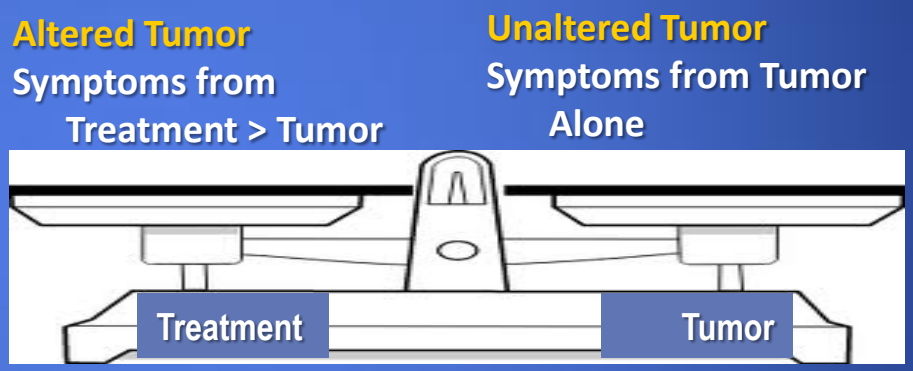
Evidenced-Based Advances in Symptom-Directed Treatment

- MODEL: MALIGNANT GLIOMA PATIENTS, HOWEVER THESE TREATMENTS ARE GERMAINE TO MOST CNS TUMORS CARED FOR BY NEUROSURGEONS
- Disease Modeling & Prognostication
- Performance Status
  - Assessment
  - Stratification
  - Optimization
- Toxicity prevention & mitigation
  - Tumor-related
  - Treatment-related
- Manage specific symptoms
- Surveillance protocols
  - Tumor progression
  - Delayed sequel of treatment (survivorship)



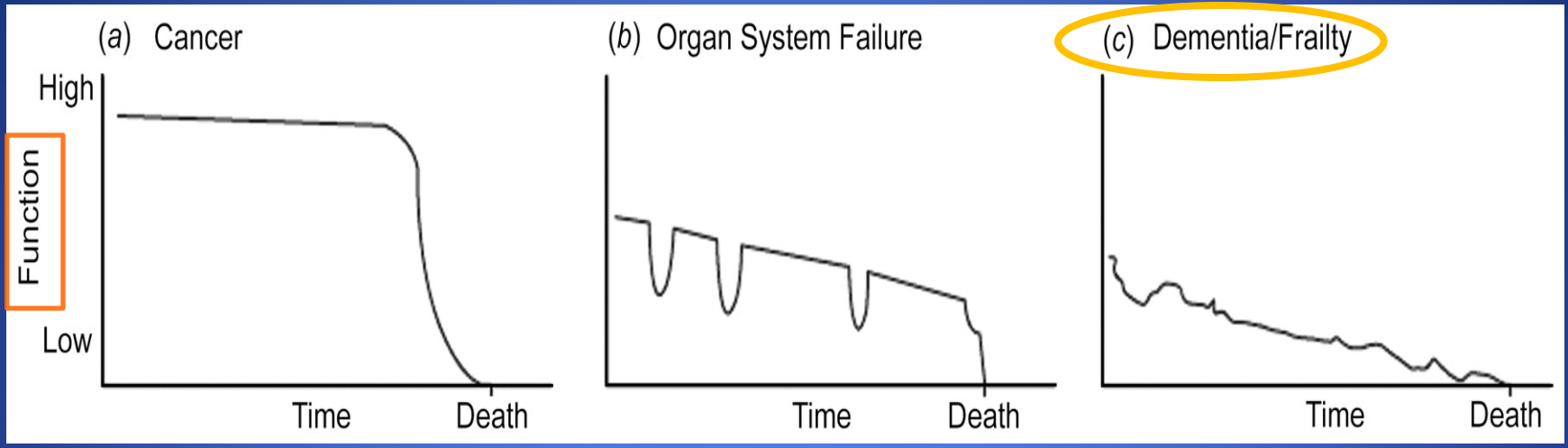
Evidenced-Based Symptom-Directed (Palliative Treatment)





- Only a fraction of Malignant Giomas are “cured” and none are “asymptomatic” across a lifetime
- Thus, an essential part of treatment must include **evidenced-based symptom-directed (palliative) treatment**

Historical Illness Trajectory in Malignant Gliomas

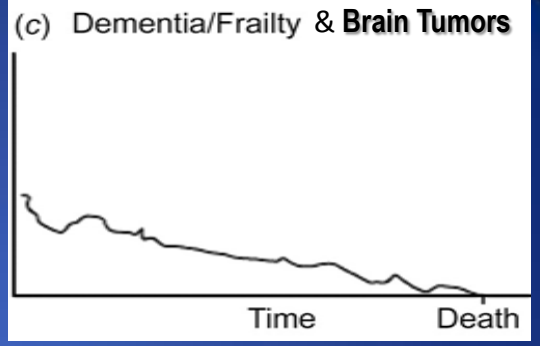


- Malignant Gliomas historically follow the trajectory of unremitting, progressive neurologic diseases
- Criteria for entering Palliative Care & Hospice programs should follow such diseases, not systemic cancers
- **Evidenced-Based symptom-directed treatments are changing this illness trajectory!**

Piedmont Brain Tumor Center

Adapted from Various Palliative Care Models, JAMA, '01

Optimizing Treatment Requires Individualizing Goals of Care Across the Continuum of Life



100%
ALWAYS

CARE

Tumor-directed

"Trauma"

Symptom-directed (palliative)

End of Life

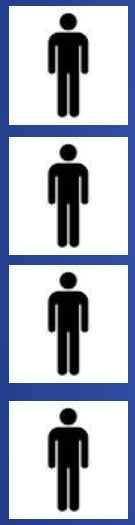
Pre-Bereavement

LIFE CONTINUUM

Individualized Treatment Over a Life Continuum

Analogous to Writing a Novel Together

"Chapters in Care"



XXXXX----------OOOOO.....?

XXXXXXXXXXXX-----OOOOOOOOOOOO.....?

XX--------OOOOOOOO.....?

XXXXXXXXXXXXXXXXX----------OOO.....?

- Add as many "pages" to each chapter
- Be smart & efficient at changing chapters
- Maintain many good next options

The "Binder" of the novel is one's KPS and Quality of Life

Evidenced-Based Advances in Symptom-Directed Treatment

- Disease Modeling & Prognostication
- Performance Status
  - Assessment
  - Stratification
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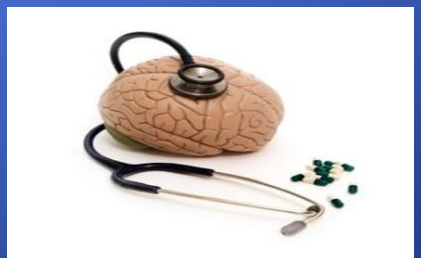


Karnofsky Performance Status (KPS)

Value	Level of Functional Capacity
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self, unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Hospitalization is necessary, very sick, active supportive treatment necessary
10	Moribund, fatal processes progressing rapidly
0	Dead

Red lines= typical cut-off for routine & investigational treatment

Oken, M, 1979; Crooks, V, J Gerontol. 1991; de Haan R, Stroke. 1993; Hollen PJ, Cancer. 1994; O'Toole DM, West J Med. 1991; Schag CC,JCO, 1984

ECOG Performance Status (PS)

- 0-Fully active, able to carry on all pre-disease performance
- 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
- 2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about > 50%
- 3-Capable of only limited self-care, confined to bed or chair > 50%
- 4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5-Dead
- Red line = typical cut-off for routine & investigational treatment

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Neurologic Functional Status

- 1. No neurologic symptoms; fully active at home/work without assistance
- 2. Minor neurological symptoms, fully active at home/work without assistance
- 3. Moderate neurological symptoms, less than fully active at home/work and requires assistance
- 4. Severe neurological symptoms, totally inactive requiring complete assistance at home or in institution, unable to work.

www.rtog.org ; others

RPA - Glioma

- **III:** Glioblastoma, KPS 0, age <50
- **IV:** Glioblastoma, KPS 1-2, age <50
- **V:** Glioblastoma, age >50, biopsy-only

Mirimanoff, JCO, 2006; Scott CB, IJROBP, 1998; Curren W, JNCI, 1993

Proposed: Charlson Comorbidity Index

- Ening et al, Retrospective review of 233 new adult Glioblastoma patients at a single tertiary institution in Germany from 2006-2011.
- **METHODS:**
- Age, gender, signs, symptoms, KPS, tumor characterisics (size, location, IDH-mutation status, and MGMT-pomoter methylation status), treatment parameters (volumetric EOR and adjuvant therapy).
- Comorbidity status quantified by the Charlson comorbidity index
- Survival analysis by the Kaplan-Maier method. Influence of variables by log-rank test.
- **RESULTS:**
- Patients of age > 65 years, KPS ≤ 70, and CCI > 3 were significantly associated with both poor OS (all $p < 0.0001$).
- Patients of age > 65 years significantly had a CCI > 3 ($p < 0.0001$).
- **CONCLUSIONS:**
- Confirms established prognostic parameters (age and KPS) for Glioblastoma outcome.
- The CCI significantly impacted outcome and may assist pre-operative stratification.

Ening G et al, J Cancer Res Clin Oncol. 2015

KPS is King

- Independent prognostic factor
  - At diagnosis
    - overall survival
  - At pre-1st resection, adjuvant therapy, pre-2nd resection
    - Overall survival
    - Quality of life
- Essential to receive treatment
  - clinical trials
  - routine therapy
- Essential in a Neurosurgeon's discernment on the survival/functional benefits to subsequent resections
  - EOR may be correlated to IDH-1/2-mutation and other molecular-genetic aberrations
- Score is reported differently by provider, caregiver, patient

Sacko A, et al, J Neurooncol. 2015 ; Stark AM, et al, Clin Neurol Neurosurg. 2012 ; Kumar N et al, J Neurosci Rural Pract. 2013; Kumar N et al, J Neurosci Rural Pract. 2013 ; Dunbar et al, JCO, 2007

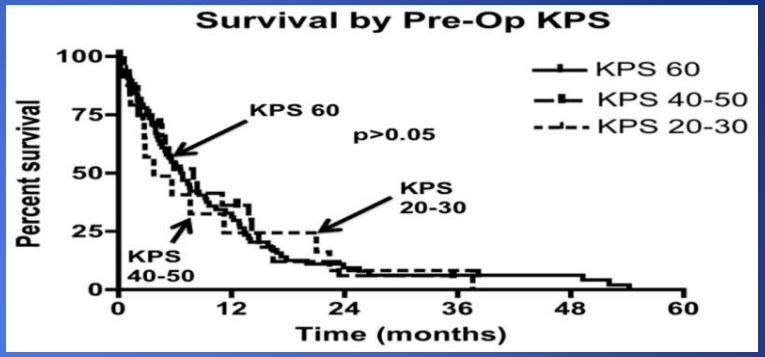
KPS in Recent Literature

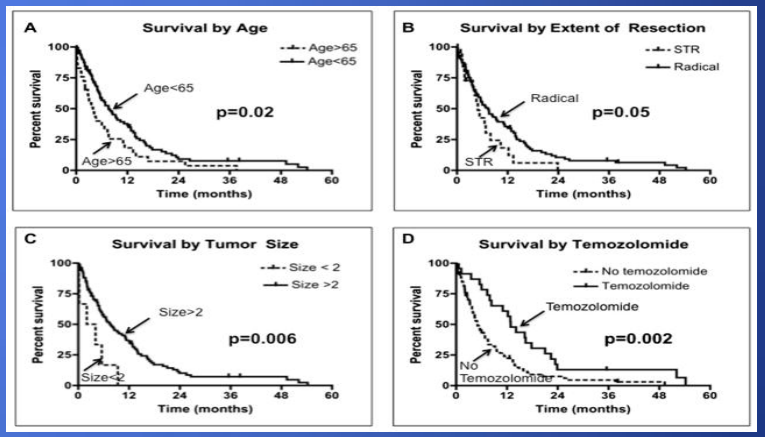
KPS in time	Authors	Nuances
At Diagnosis	Stark AM, Clin Neurol Neurosurg. 2012	
	Raysi Dehcordi S et al, J Neurosurg Sci. 2012	also affective d/o effects OS
	Gathinji M et al, Surg Neurol. 2009	Association of preoperative depression and survival after resection of malignant brain astrocytoma.
Pre-1st resection		
	Ening G et al, J Cancer Res Clin Oncol. 2015	Charlson comorbidity index
	Chaichana KL et al, World Neurosurg. 2014	achieving a decreased RV and/or an increased EOR is independently associated with survival and recurrence in those patients with tumors with similar resection capacities.
		idh status improves survival in aggressive resections/CE and nonCE. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal
	Beiko J et al, Neuro Oncol. 2014	surgical resection.
	Tanaka S et al, J Neurosurg. 2013	elderly age alone not prevent decisions of sx vs biopsy b/c also benefit
	Sanai N et al, J Neurosurg. 2011	
	Kumar N et al, J Neurosci Rural Pract. 2013;	associated with certain molec./genetic aberrations
	Chaichana KL et al, J Clin Neurosci. 2013	pre-op poor kps - aggressive resection improved post-op kps/os, outcomes and factors associated with survival for poor functioning patients who underwent aggressive resection of their GB
Adjuvant Tx (ability	Chaichana KL et al, J Neurosurg. 2011	
	Sacko A et al, J Neurooncol. 2015	KPS > 70 for >73% survival

Adjuvant Tx (ability	Chaichana KL et al, J Neurosurg. 2011	patients who underwent aggressive resection of their GB
	Sacko A et al, J Neurooncol. 2015	KPS > 70 for >73% survival
	Sun MZ et al, J Neurosurg. 2015	modest delay in time to chemo/RT did not impact OS or KPS
	Han SJ et al, Neurosurgery. 2015	A short delay in the start of concurrent chemoradiation is beyond the classic paradigm of 4 weeks post-resection and may be associated with prolonged OS and PFS.
	Michaelsen SR et al, BMC Cancer. 2013	correlation related to dex dose/duration
	Barbagallo GM et al, Neurosurg Focus. 2014	kps not lowered with longterm tmz
Pre-2nd resection		
	Oppenlander ME et al, J Neurosurg. 2014	as long as kps maintained/no worse neuro fxn, then >80% eor improved survival/outcome. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. For recurrent glioblastomas, an improvement in overall survival can be attained beyond an 80% EOR. This survival benefit must be balanced against the risk of neurological morbidity, which does increase with more aggressive cytoreduction, but only in the early postoperative period. Interestingly, this putative EOR threshold closely approximates that reported for newly diagnosed glioblastomas,
Tx at recurrence		
	Bloch O et al, J Neurosurg. 2012	aggressive resection at 1st rec improves os/kps if gtr achieved, regardless if initial sx was STR
	Carpentier AF et al, Eur J Neurol. 2012	Steroid-sparing effects of angiotensin-II inhibitors in glioblastoma patients. Lower dex = improved kps/os. Avastin improved qol
	Hofer S et al, Acta Oncol. 2011	avastin as valuable palliation with preservation of KPS and an option for steroid withdrawal in patients treated with BEV, supporting the role of this therapy in late-stage disease.

Example: Survival by Pre-operative KPS

- N=100 new Glioblastoma patients, focus: < 60 or > 60 KPS
- observational, 1997-'07, JHH
- **Goal: factors associated with survival for "poor functioning" < 60 KPS patients undergoing aggressive resections**
- Factors associated with improved survival were age <65 year (p = 0.005), tumor size >2 cm (p = 0.01), radical tumor resection (p=0.01), and temozolomide (p = 0.001).
- This study identifies a subset of patients with poor functional status who may benefit from aggressive surgical resection.





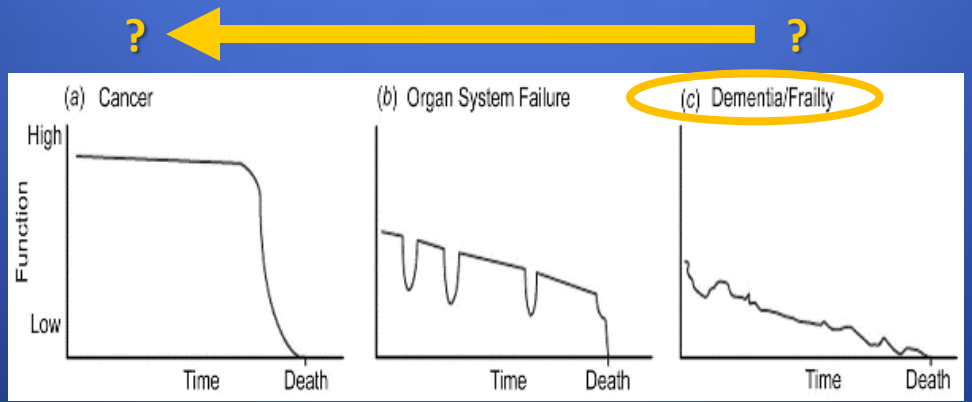
Multivariate associations with survival

Variables	Relative risk (95% CI)	*p* value
Factors associated with improved survival		
Decreasing age	0.985 (0.969–0.995)	**0.05**
Age <65 years	0.455 (0.275–0.779)	**0.005**
Tumor size >2 cm	0.269 (0.119–0.722)	**0.01**
Radical resection	0.415 (0.226–0.798)	**0.01**
Temozolomide	0.465 (0.274–0.756)	**0.001**
Factors notably not associated with survival		
Preoperative KPS score	0.996 (0.980–1.014)	0.66
RPA IV	0.860 (0.544–1.325)	0.50
RPA V	1.136 (0.752–1.741)	0.55
RPA VI	1.125 (0.501–2.186)	0.75
Motor deficit	0.846 (0.546–1.270)	0.42
Language deficit	0.733 (0.447–1.156)	0.19
Recurrent GB	0.921 (0.584–1.424)	0.71

Chaichana KL et al, J Clin Neurosci. 2013

KPS Evolves over Lifetime

- Sacko A, et al, J Neurooncol. 2015
- N=84, prospective, French institution
- Median survival with KPS ≥ 70 was 14.5 months.
- Patients spent an avg. of 73 % of their lifespan with a KPS ≥ 70.
- Surgical resection and low steroid dosage were statistically associated with increased survival time with KPS ≥ 70 ($p = 0.015$ and $p = 0.03$, respectively)
- Median survival with KPS ≥ 70 largely exceeds PFS.



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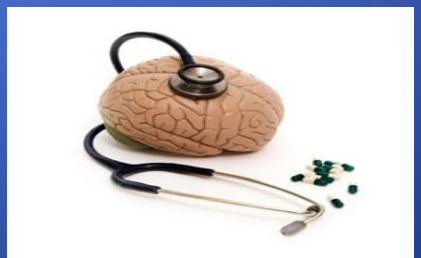

Specific Symptom Examples

CNS Anatomy & Function

- Cerebral Edema
- Thrombosis, Hemorrhage
- Obstruction, NPH
- Seizures
- Cognition, Mood, Coping
- Neurologic Deficits, Pain
- Immunosuppression

"Ask your doctor is taking a pill to solve all your problems is right for you"

ASCO POST, 6/2011

Iatrogenic & Co-morbid

- Immunosuppression
- Infection, myelosuppression
- Insomnia
- Endocrine, metabolic
- Fatigue, myopathy
- Drug toxicity
- Fertility, family planning, intimacy, libido
- Unrelated co-morbidities

KEY: Pursue reversible causes and aggressively treat

Hughes, MA 05; Chang, S JAMA 05; Risk Stratification: Armstrong, Neuro-Onc, 2010

Specific Symptom Examples

CNS Anatomy & Function

- Cerebral Edema
- Thrombosis, Hemorrhage
- Mobility, Deconditioning
- Seizures
- Cognition, Mood, Coping
- Neurologic Deficits, Pain
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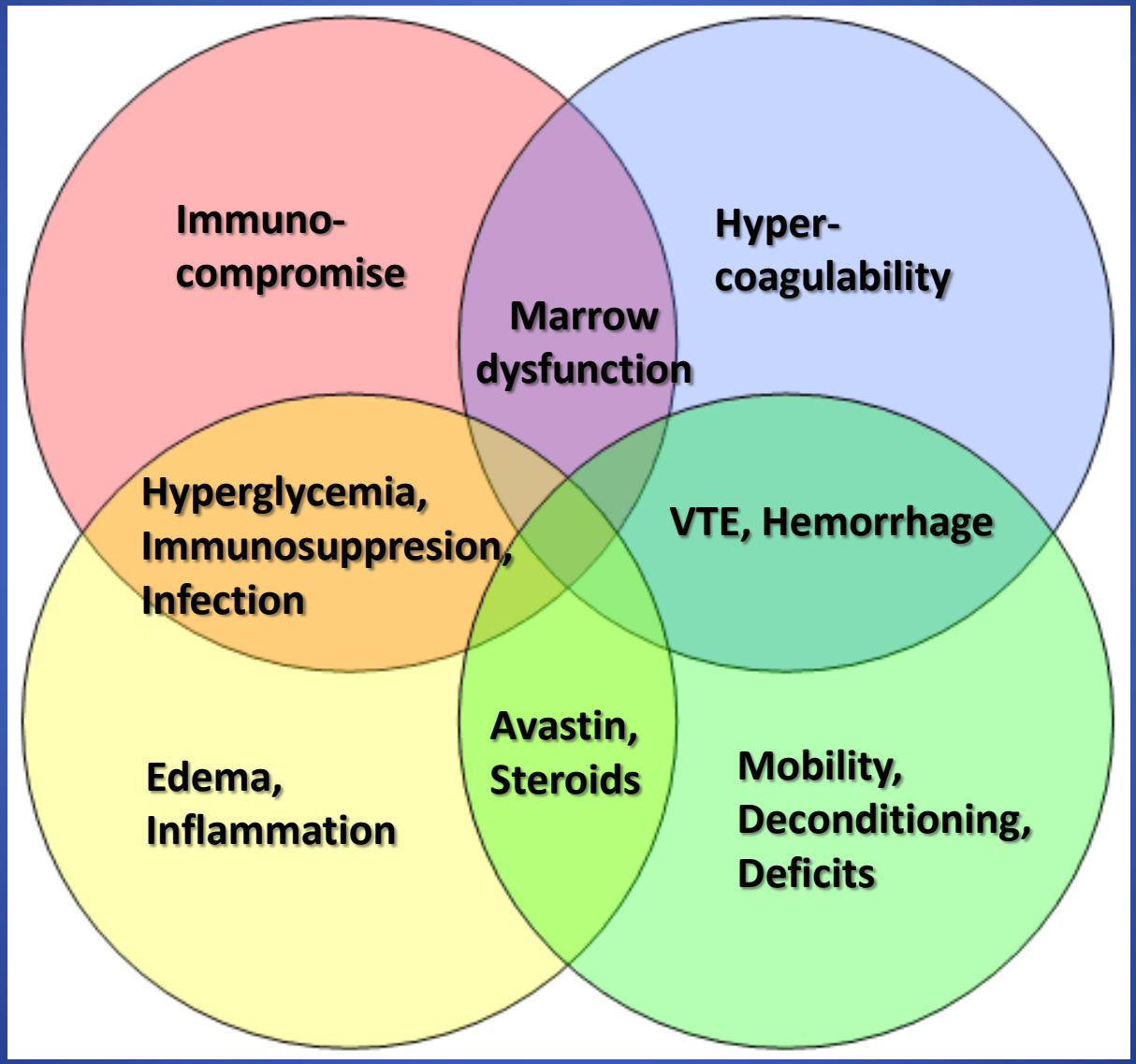
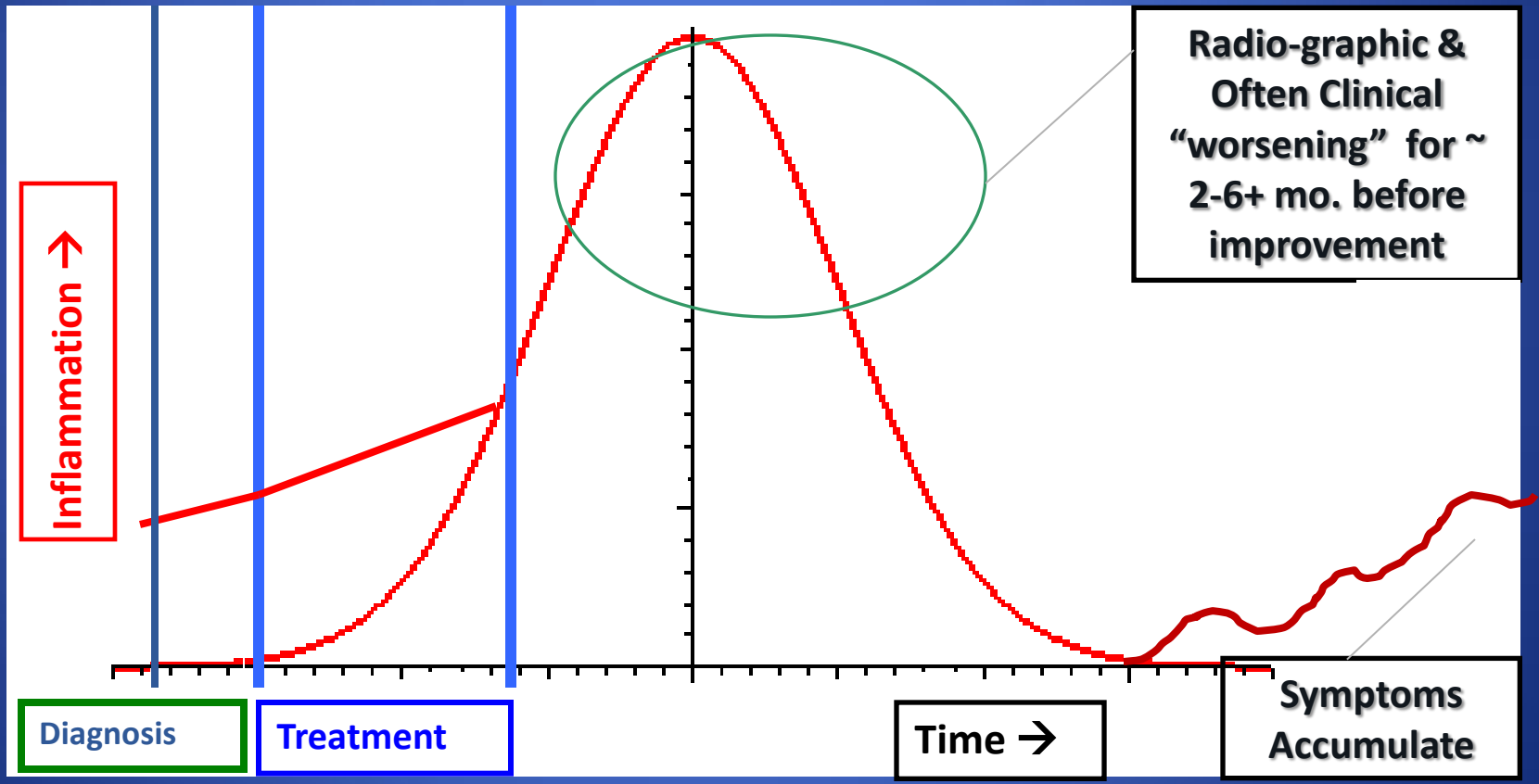
Hughes, MA 05; Chang, S JAMA 05; Risk Stratification: Armstrong, Neuro-Onc, 2010; Benson, NEJM, '70; Dunbar, EM, Cibula, ANO, '11

Symptom-Directed Treatment



Symptoms & KPS Evolution Requires Ongoing Treatment

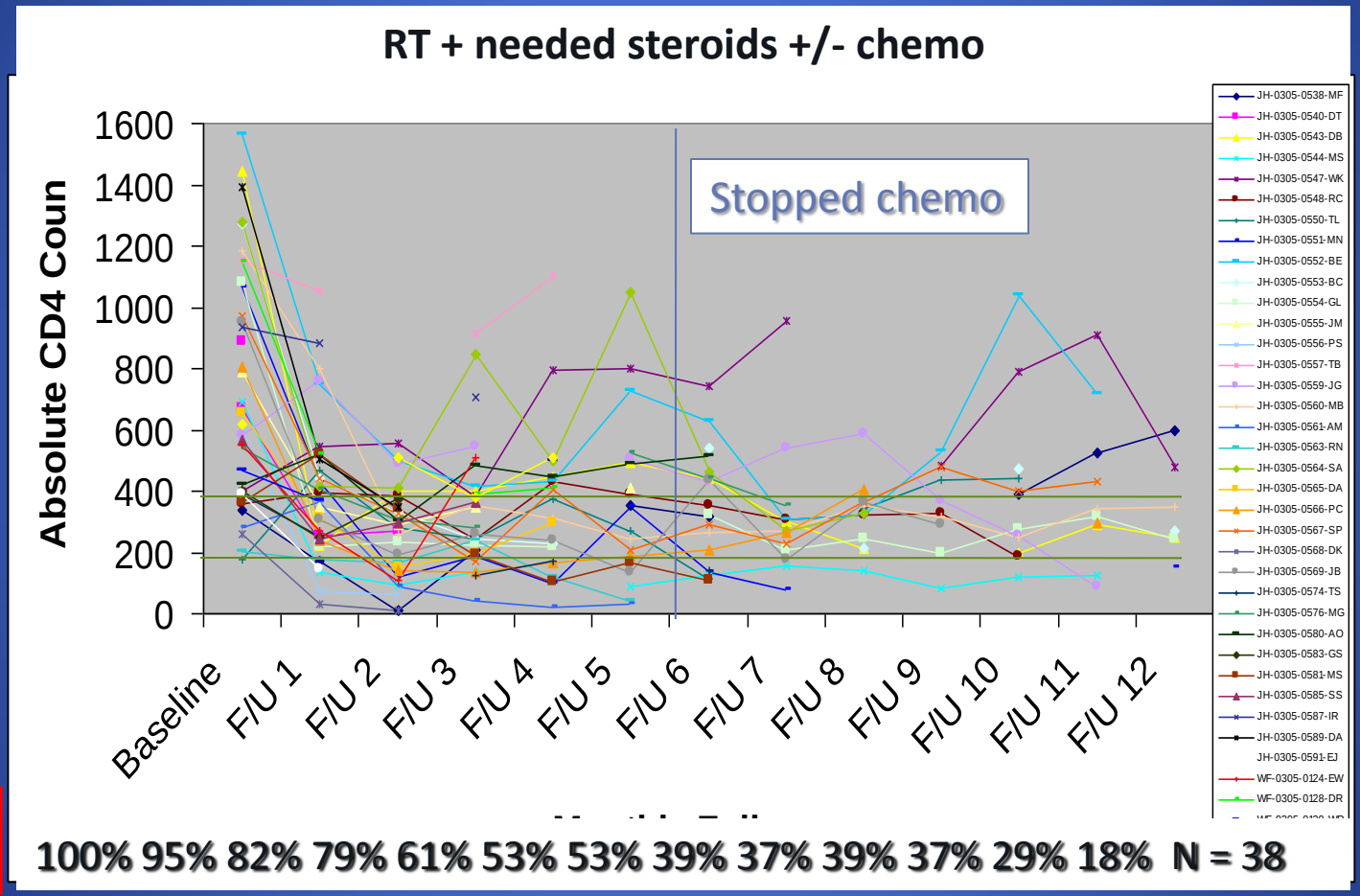


Steroids

- No consensus in management [Deutch MB et al, J Neurooncol. 2013; Chang SM et al, JAMA, 2005]
- Decadron is best for CNS
  - More glucocorticoid, Less mineralocorticoid [various]
  - BID frequency is sufficient
  - Plethora of short and long-term SEs
  - Cumulative dose correlated to lower KPS and OS [Michaelsen SR et al, BMC Cancer. 2013]
- Hyperglycemia correlated to:
  - Lower OS [Mayer A et al, Strahlenther Onkol. 2014; McGirt MJ et al, Neurosurgery. 2008]
  - Infections [Derr RL, et al, J Clin Oncol. 2009; Hughes MA et al, IJBROP, 2005]
  - Post-operative function loss in patients w/ primary eloquent glioblastomas [Link TW, et al, J Clin Neurosci. 2012]
- Strategies to minimize hyperglycemia include:
  - (Modified) Ketogenic diet [Champ CE et al, J Neurooncol. 2014; Blakeley et al, JNO, in-press]
  - Non-steroid "alternatives" are not adequate – e.g., mannitol, diamox, loop diuretics, VEGF agents, trial agents [Wen, P, et al, Neuro 08; Aenlle, L, Kesari, S, Dunbar, EM, ANO, '11, Dunbar; various]

Immunosuppression

Example: Lymphopenia from Glioma, Steroids, RT, etc..



HIV

AIDs

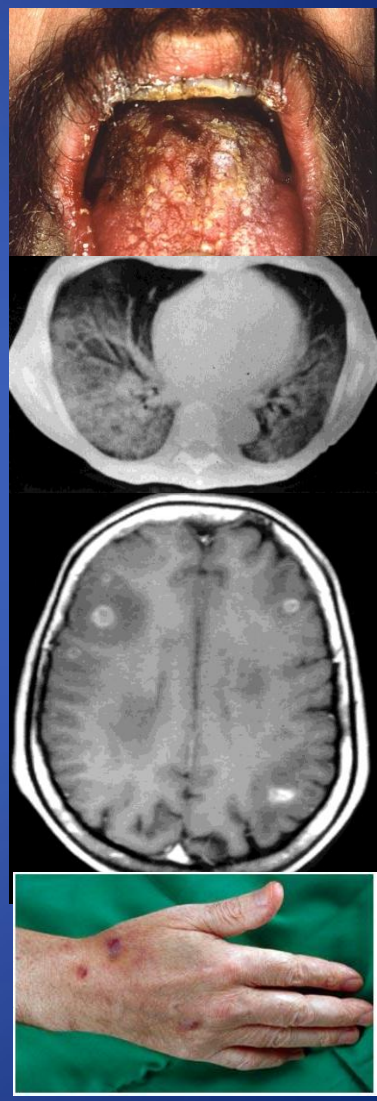
% on study: 100% 95% 82% 79% 61% 53% 53% 39% 37% 39% 37% 29% 18% N = 38

Consider CD4 count; Bactrim, Dapsone, Pentamidine

Dunbar, E, Grossman, SA, NOIU, used by permission, 06

Lymphopenia-related Infections

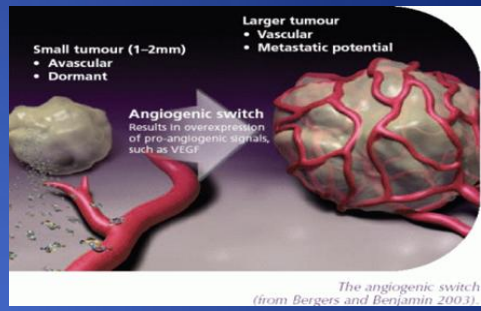
- Pneumonia (community-acquired), PJP (PCP)), Candida, Legionella, Listeria [Neuwelt AJ, et al, CNS Oncol.2014; various]
- Fungal, atypicals, parasites, less likely bacteria
- Viruses, e.g., CMV, Zoster, Hepatitis, Pertussis/Diphtheria
- U.S. Standard Practice: PJP prophylaxis in Malignant Gliomas undergoing RT (regardless of steroids, chemo):
  - Bactrim improves OS and lowers infections, including hospitalizations *[Hughes MA et al, IJROBP, 2005; various]*
- Hepatitis B & C reactivation correlated to steroids, immunosuppression [Grieco A et al, Medicine (Baltimore). 2015; Sarganas G et al, Neuro Oncol. 2012]
- Non-infectious hepatitis correlated to temozolomide +/- concurrent AEDs (valproic acid) [Grieco A et al, Medicine (Baltimore). 2015; Neyns B et al, Acta Neurol Belg. 2008]

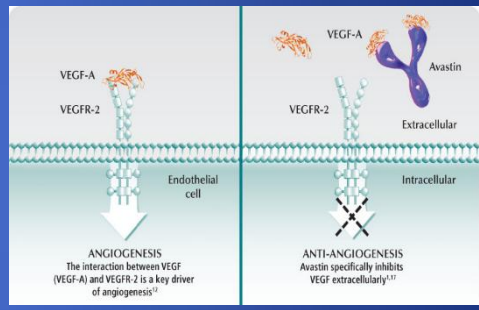


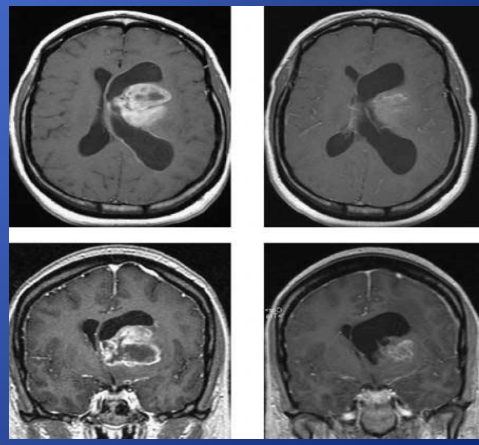
emedicine.medscape.com;

VEGF Agents

- The VEGF pathway is key to both angiogenesis and vascular permeability
- Alters the Blood Brain Barrier
  - T1-CE MRI, Vasogenic Edema & Mass-effect
- Tumor-directed roles:
  - 2009 U.S. FDA approved Monoclonal Ab against the extracellular VEGF-R in for progressed Glioblastoma, based on RR & PFS. Wide extrapolation
  - RCTs and other data sets confirm an absence of survival benefit for new Glioblastoma [Neagu MR, et al, Curr Treat Options Neurol. 2015; Avalio, RTOG0525; Khasraw M et al, Cochrane Database Syst Rev. 2014]
  - Clinical trials are focusing on overcoming resistance patterns and maximizing mechanisms



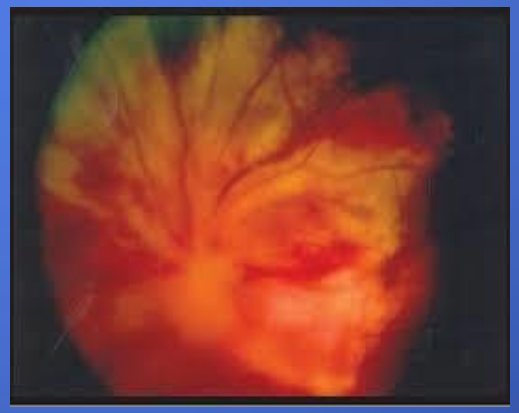


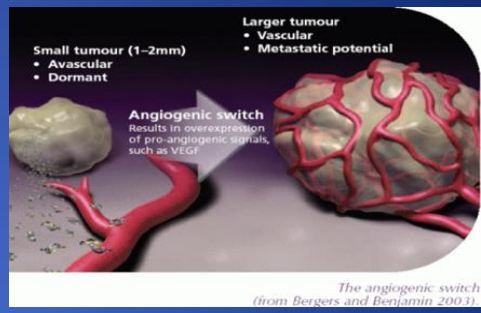


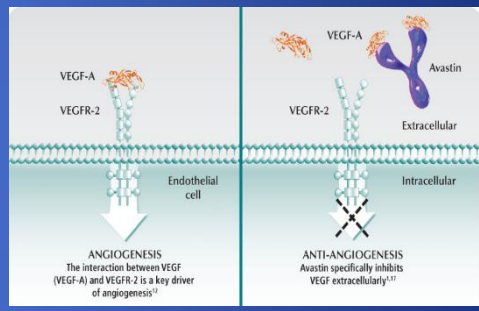
Vredenburg JJ, CCR 07 and JCO 07

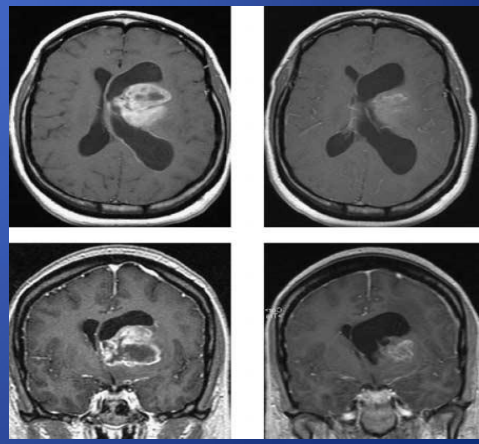
VEGF Agents

- Symptom-directed (Palliative) roles:
  - Often improving KPS and quality of life in progressed or highly-symptomatic Glioma [Khasraw M et al, Cochrane Database Syst Rev. 2014 ; Hofer S, et al, Acta Oncol. 2011]
  - "Steroid-sparing" for edema [Roth P et al, Expert Rev Anticancer Ther.2013 ; Carpentier AF, Eur J Neurol. 2012 ; Hofer S, et al, Acta Oncol. 2011 various]
  - Radiation-necrosis, vasculopathy
  - Angioedema
  - Macular degeneration
- Expensive!
- Altered patterns of imaging, progression and resistance
  - * RANO criteria [Chang, et al, N-O, 07; various]





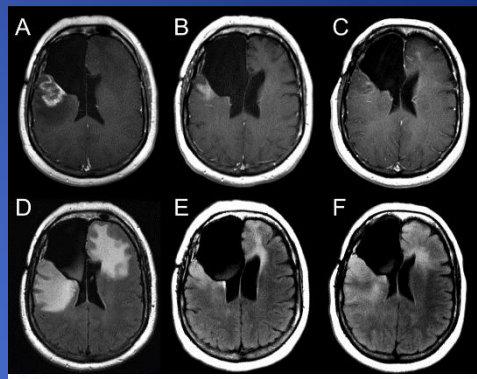


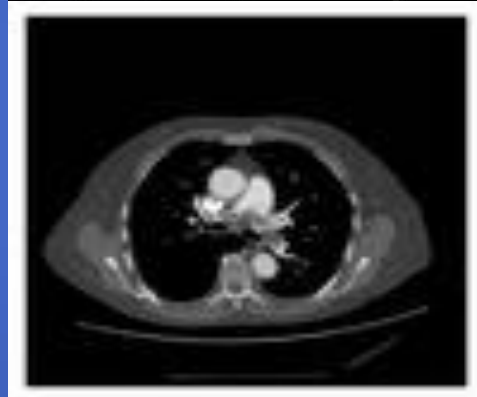


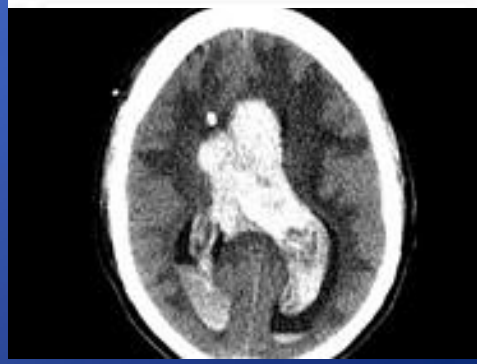
Vredenburg JJ, CCR 07 and JCO 07

VEGF Agents

- Unique safety & monitoring
  - Not a “chemo”
  - ~21-28 D ½ life of “vascular sequela”, including de novo arterial/venous hemorrhage, thrombosis; acceleration of CVA, CAD, HTN, vascular renal dz; wound dehiscence, & poor wound healing, fatigue, PML, etc..
  - No “antidote”
  - Peri-Surgical Safety:
    - Hold ~28 days for major elective surgery (a minimum of 4-6 wks if 2nd Glioma resection)
    - Hold ~14 days for minor surgery [various]
  - ? Effect on fertility







Vredenburg JJ, CCR 07 and JCO 07; http://imagebank.hematology.org/Content%5C672%5C3671/3671_t.JPG

VTE & Hemorrhage

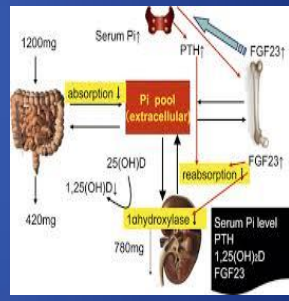
- STUPP protocol: 20% mild thrombocytopenia and 5% have severe [Stupp R et al, 2005]
- VTE & hemorrhage occur in ≤ 35% of Malignant Gliomas [Chang SM, JAMA, 2005; various]
- To-date industry trials evaluating prophylactic LMWH in new Glioblastoma have been stopped 2/2 increased hemorrhage and/or lack of efficacy
- Modern algorithms for VTE and hemorrhage in CNS tumor patients are minimizing toxicity [Strowd RE 3rd, et al, Curr Treat Options Onc. 2012; Gerber DE et al, JCO, 2006]
- Modern use of LMWH may be improving outcomes [Zincircioglu SB et al, J BUON. 2012]
- Newer mechanisms of AC may be more safe and efficacious, e.g., Direct-thrombin-inhibitors [www.uptodate.com; Expert Review of Neurotherapeutics, Morales-Vidal S et al, 2012]
- Mounting evidence of safety of VEGF Agents in patients with treated Glioma, mets, related [Norden AD et al, J Neurooncol. 2012; Nghiemphu P et al, N-O, 2008; various]
  - After 4-6 from last resection
  - On AC for VTE (after acute) or after SDH/SAH (after acute)
  - -On anti-PLT therapy
- Alternatives or adjuncts include: compression stockings, intermittent compression devices, and minimizing steroids, inflammation, trauma [various]

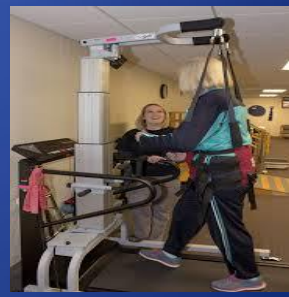
Other Symptoms with Increasing Evidence-Based Treatment

Cognition, Memory, Mood, Motility (2nd Parkinsonism), Sleep Disorders, Fatigue, Hypersomnolence:

- Reversible acetylcholinesterase inhibitors
  - Donepezil
- NMDA receptor blockers
  - memantine
- Central (psycho)-stimulants
  - Methylphenidate & Modafinil
- Dopamine-Agents
  - Methylphenidate
  - Levo-Dopa & Similar
- Serotonin-Norepinephrine Re-Uptake Inhibitors
- Sleep continuity agents
- Neuropathic pain agents
  - Gabapentin, pregabalin

Nausea, Endocrine, Bone Health, Fall-prevention, Cataracts, etc.





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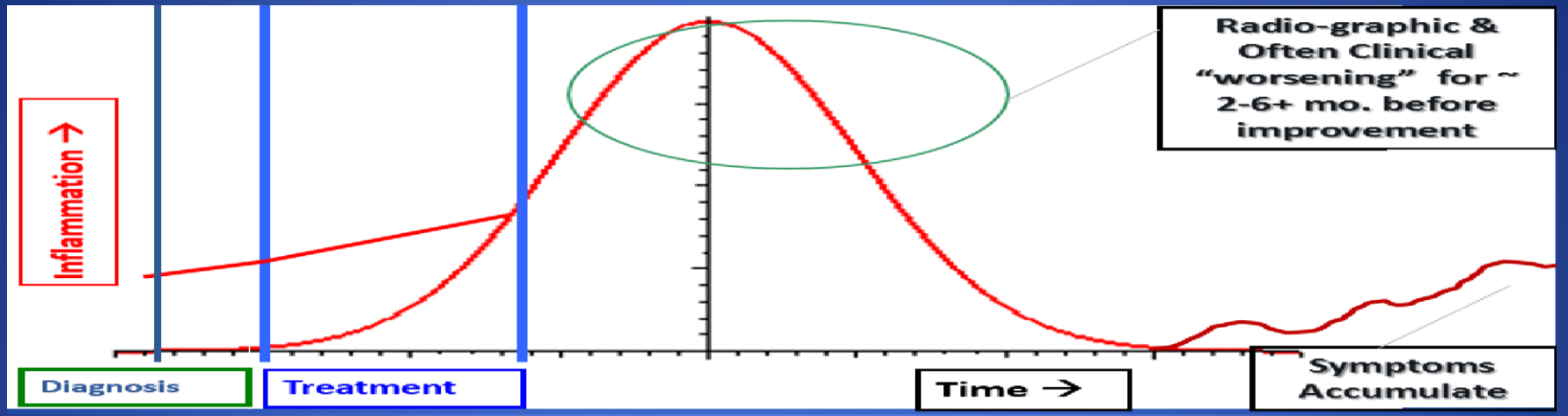
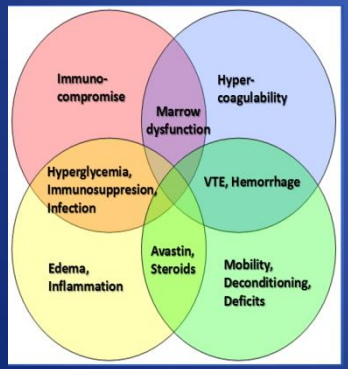
Summary of Treatments that Impact Symptoms & KPS Through Time



- Hepatitis +/- viral titers
- Vaccines

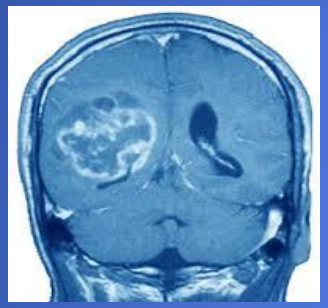


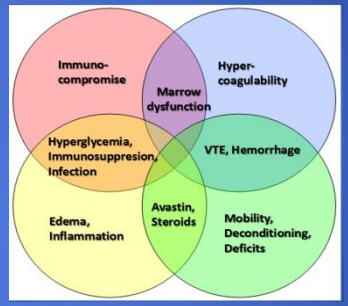
- CBC/diff q wk
- PJP prophylaxis
- +/- CMP (Glucose, TAs)
- +/- AED levels
- Least-needed Decadron
- Mobility, Conditioning
- H&Ps by experienced providers (VTE, hemorrhage, infections, etc..)

- CBC/diff q ~ mo.
- +/- PJP prophylaxis
- H&Ps by experienced providers (progression vs. pseudo-progression, delayed sequel of treatments)
- Endocrine, bone density, cataracts, emotional, etc.
- Eye, rtn to wk/drive evals.
- Fertility, libido, etc..

The End

Evidenced-Based
Symptom-Directed Treatments





Questions?

Erin M. Dunbar, MD

Director, Neuro-Oncology, Piedmont Brain Tumor Center

Member, MD Anderson Provider Network

Palliative & Hospice Medicine, Medical-Oncology, PAH, Atlanta, GA

erin.dunbar@piedmont.org

Cell: 1-404-858-7317