Management of Medical and Neurologic Complications in Cancer Patients

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DISCLOSURES

Research Support

- Agios, Astra Zeneca, Beigene, Eli Lily, Genentech/Roche, Karyopharm, Kazia, Merck, Novartis, Oncoceutics, Sanofi-Aventis, Vascular Biogenics, VBI Vaccines

Advisory Board

- Abbvie, Astra Zeneca, Agios, Bayer, Genentech/Roche, GW Pharmaceuticals, Immunomic Therapeutics, Kadmon, Puma, Taiho, Vascular Biogenics,

Speaker

- Merck, Prime Oncology

DSMB

- Tocagen

Editor

- UpToDate, Elsevier

Outline

- Anti-Epileptic Drugs
- Peritumoral edema
- Venous Thromboembolic Disease
- Miscellaneous
  - Fatigue
  - Cognitive difficulties

Incidence And Risk Factors Of Epilepsy Across Brain Tumor Types

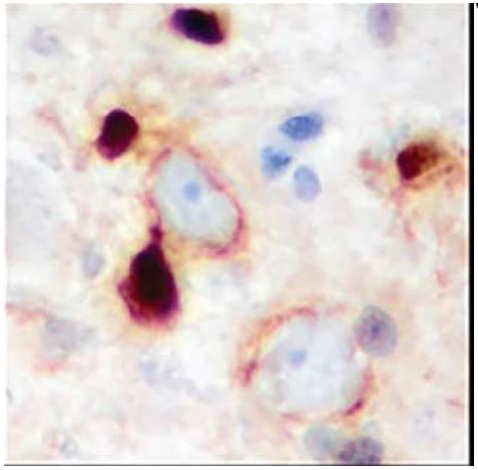
Tumor type	Approximate incidence of seizures	Risk factor for seizures	References
Glioneuronal tumors	70–80%	Frontotemporal, insular	Aronica et al. (2001); Luyken et al. (2003); Southwell et al. (2012)
Low-grade gliomas	60–75%	Frontotemporal, insular, superficial	Chang et al. (2008a); Pignatti et al. (2002); Recht and Glantz (2008); Lee et al. (2010); You et al. (2012); Iuchi et al. (2015)
High-grade gliomas	25–60%	WHO grade III, temporal lobe, superficial	Sheth (2002); van Breemen et al. (2007); Jacoby et al. (2008); Chaichana et al. (2009b); Sizoo et al. (2010)
Meningiomas	20–50%	Peritumoral edema	Yao (1994); Chow et al. (1995); Lieu and Howng (2000); Oberndorfer et al. (2002)
Metastases	20–35%	Melanoma, lung cancer	Oberndorfer et al. (2002); Lynam et al. (2007); Avila (2013)

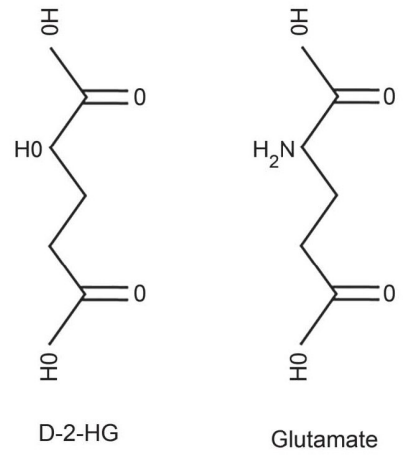
WHO, World Health Organization.

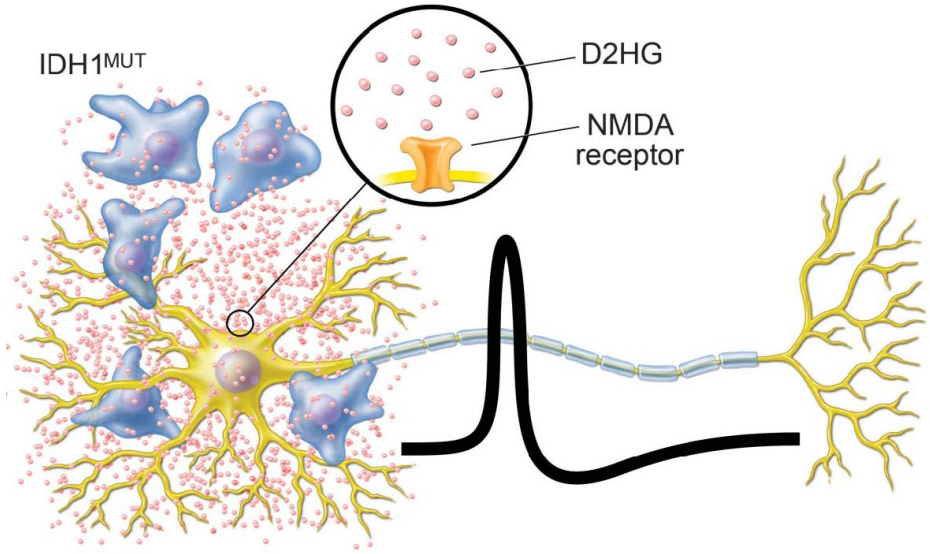
Englot et al. Handbook Clin Neurol. 2016 ; 134: 267–285.

IDH Mutated Tumors have an Increased Incidence of Seizures

Chen et al. Neurology 2017;88:1–9







- Preoperative seizures observed in 18%–34% of IDH1 wild-type (IDH1wt) patients and in 59%–74% of IDH1mut patients (p , 0.001)
- Multivariable analysis showed that IDH1mut was an independent correlate with seizures (odds ratio 2.5, 95% confidence interval 1.6–3.9, p , 0.001)
- D2HG product of IDH1mut may increase neuronal activity by mimicking the activity of glutamate on the NMDA receptor
- D2HG increased the firing rate of cultured rat cortical neurons 4- to 6-fold, but was completely blocked by AP5 (NMDA inhibitor)

Patients with seizures

- Should be treated with standard AED
- Preference for non-cytochrome P450-enzyme inducing AED
- EEG usually not necessary

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Does Valproic Acid or Levetiracetam Improve Survival in Glioblastoma? A Pooled Analysis of Prospective Clinical Trials in Newly Diagnosed Glioblastoma

2016

Caroline Happold, Thierry Gorlia, Olivier Chinot, Mark R. Gilbert, L. Burt Nabors, Wolfgang Wick, Stephanie L. Pugh, Monika Hegi, Timothy Cloughesy, Patrick Roth, David A. Reardon, James R. Perry, Minesh P. Mehta, Roger Stupp, and Michael Weller

- Results of 4 phase III trials: AVAglio, CENTRIC, CORE, RTOG0825
- VPA use at start of chemoradiotherapy was not associated with improved PFS or OS compared with other patients pooled (PFS: hazard ratio [HR], 0.91; 95% CI, 0.77 to 1.07; P = .241; OS: HR, 0.96; 95% CI, 0.80 to 1.15; P = .633)
- No association with improved outcomes was observed for levetiracetam use

AMERICAN ACADEMY OF NEUROLOGY

PRACTICE PARAMETER: ANTICONVULSANT PROPHYLAXIS IN PATIENTS WITH NEWLY DIAGNOSED BRAIN TUMORS

Report of the Quality Standards Subcommittee of the American Academy of Neurology

M.J. Glantz, MD; B.F. Cole, PhD; P.A. Forsyth, MD; L.D. Recht, MD; P.Y. Wen, MD; M.C. Chamberlain, MD; S.A. Grossman MD; and J.G. Cairncross, MD

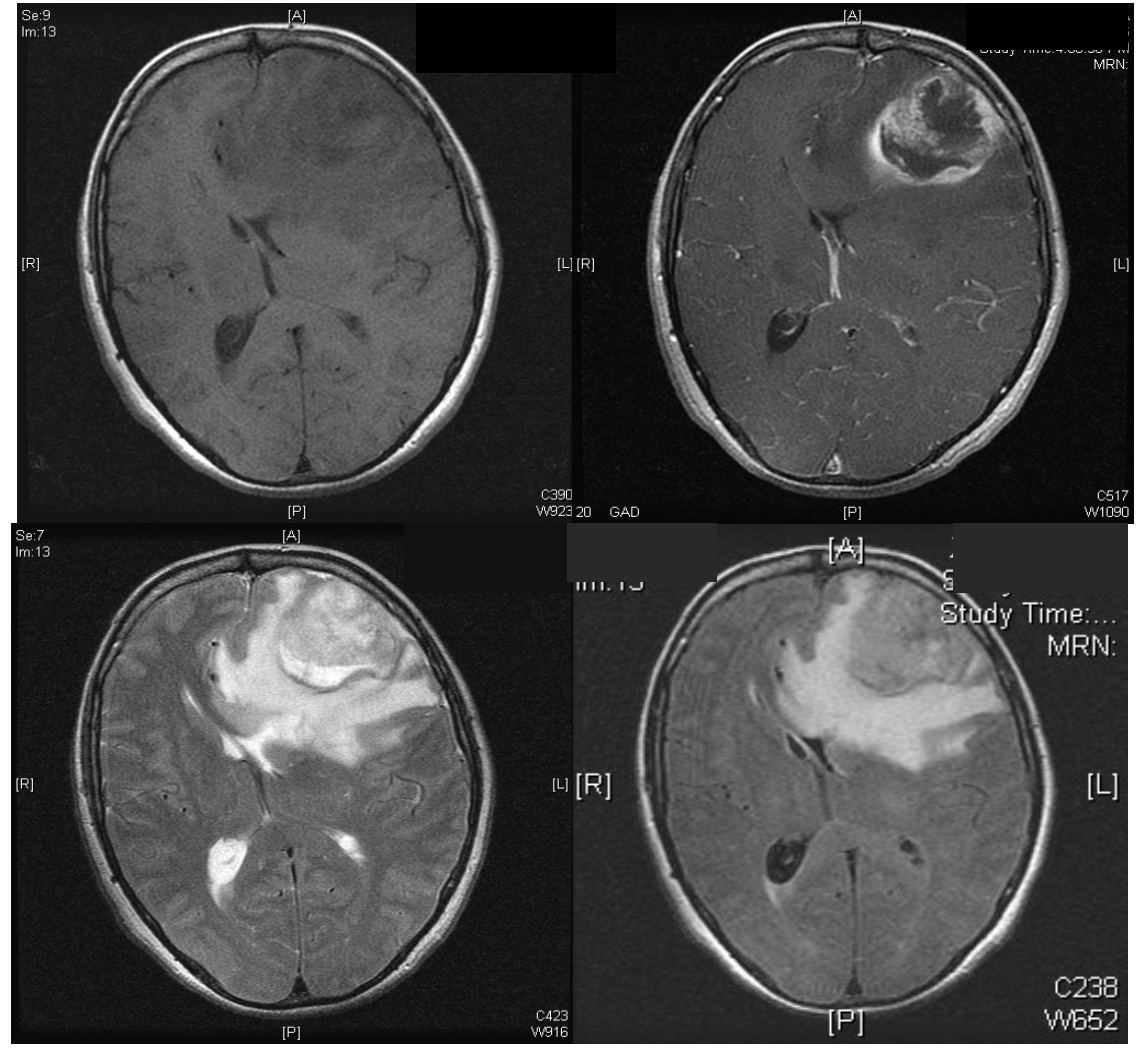
- **Glantz et al: Neurology 2000;54:1886-1893**
- No definite evidence that patients who have not had seizures benefit from prophylactic AED
- Preferable to Use non-enzyme inducing AED

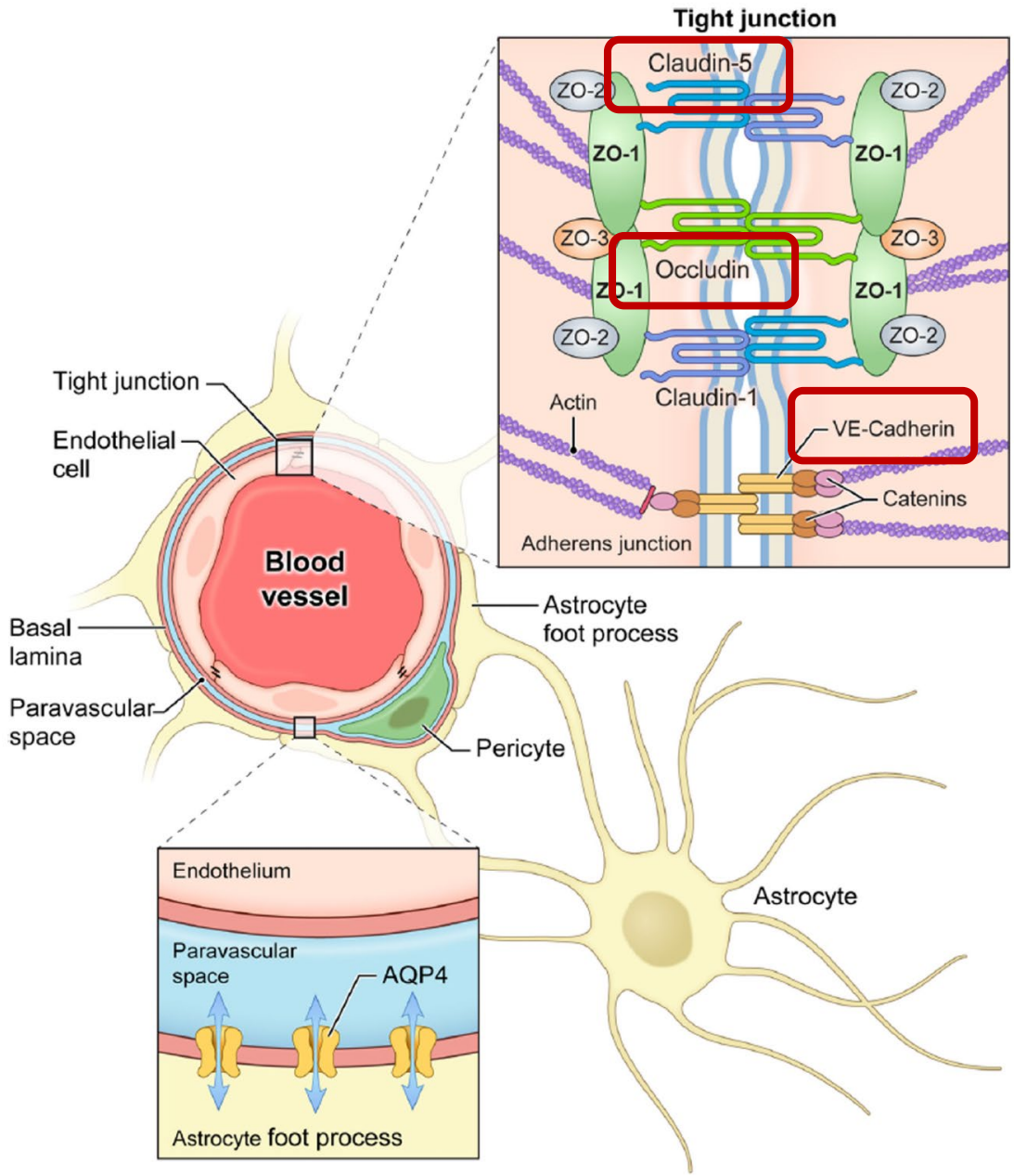
Recommendations for Anticonvulsant Therapy for Patients with Gliomas

- **Patients with Seizures**
  - Anticonvulsants
- **Patients without Seizures**
  - No definite evidence of benefit after 1st or 2nd week post-op
  - Fairly high risk of further seizures
- **Prospective randomized study needed**

Peritumoral Edema

- Glucocorticoids preferred
- Once or twice daily dosing adequate
- Use as little as possible
- Anti-VEGF therapies has reduced need for steroids





Glucocorticoids induce expression:

1) Tight junction proteins **occludin** and **claudin-5**
2) Adherens junction protein vascular endothelium cadherin **(VE-cadherin)**

Courtesy of Michael White

Neurologic Complications of Corticosteroids

- **Common**
- **Myopathy**
- **Behavioral changes**
- Visual blurring
- Tremor
- Insomnia
- Reduced taste and olfaction
- Cerebral atrophy

- **Uncommon**
- Psychosis
- Hallucinations
- Hiccups
- Dementia
- Seizures
- Dependence
- Epidural lipomatosis

Brain Advance Access published March 28, 2016

doi:10.1093/brain/aww046 BRAIN 2016: Page 1 of 14 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Corticosteroids compromise survival in glioblastoma

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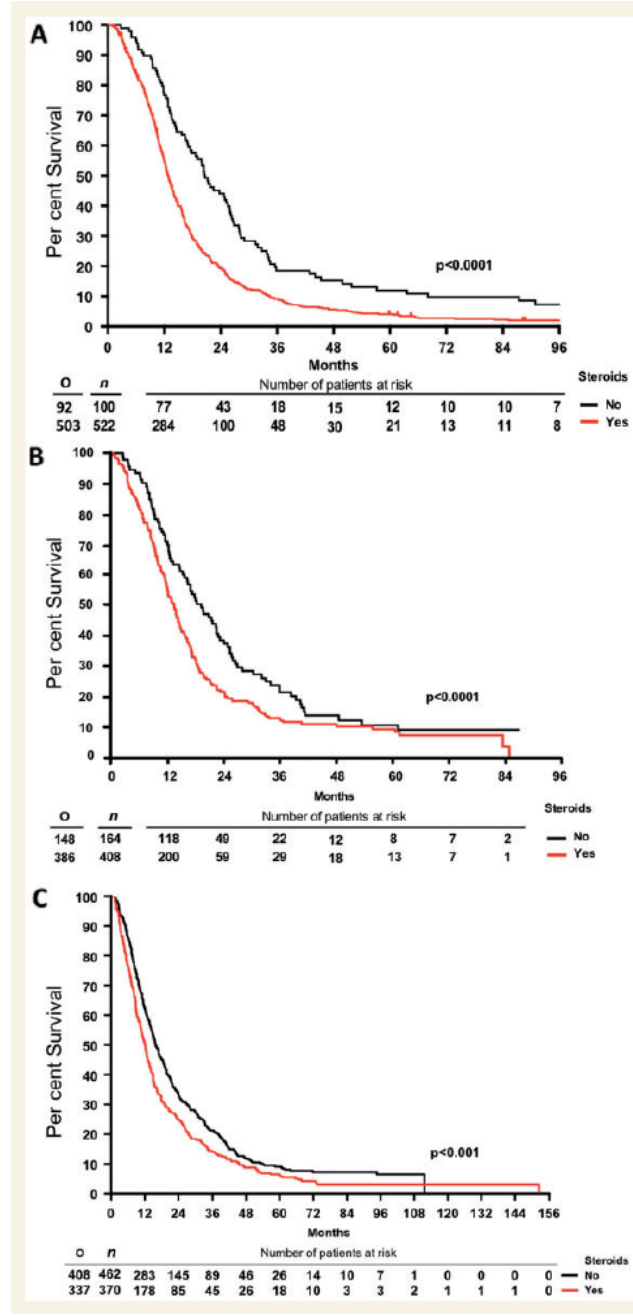

OXFORD ACADEMIC

NEUROSURGERY

THE REGISTER OF THE NEUROSURGICAL MEME

2019

Letter: When Less is More: Dexamethasone Dosing for Brain Tumors

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To the Editor:

We are writing to highlight the discrepancy in dosing schedules for corticosteroids used to treat peritumoral edema between the neurosurgical community and the neuro-oncology community and suggest that it may be time to re-evaluate the dosing of dexamethasone for brain tumors.

.....

Administering corticosteroids every 6 h frequently can result in poor sleep due to medication-related effects or medication administration itself, contributing to increased daytime fatigue. In a population where preserving the quality of life is paramount, and in the absence of evidence to justify more frequent dosing, we hope the neurosurgical community will join the neuro-oncology community and consider changing its practice to once or twice a day dosing of dexamethasone for brain tumor patients.

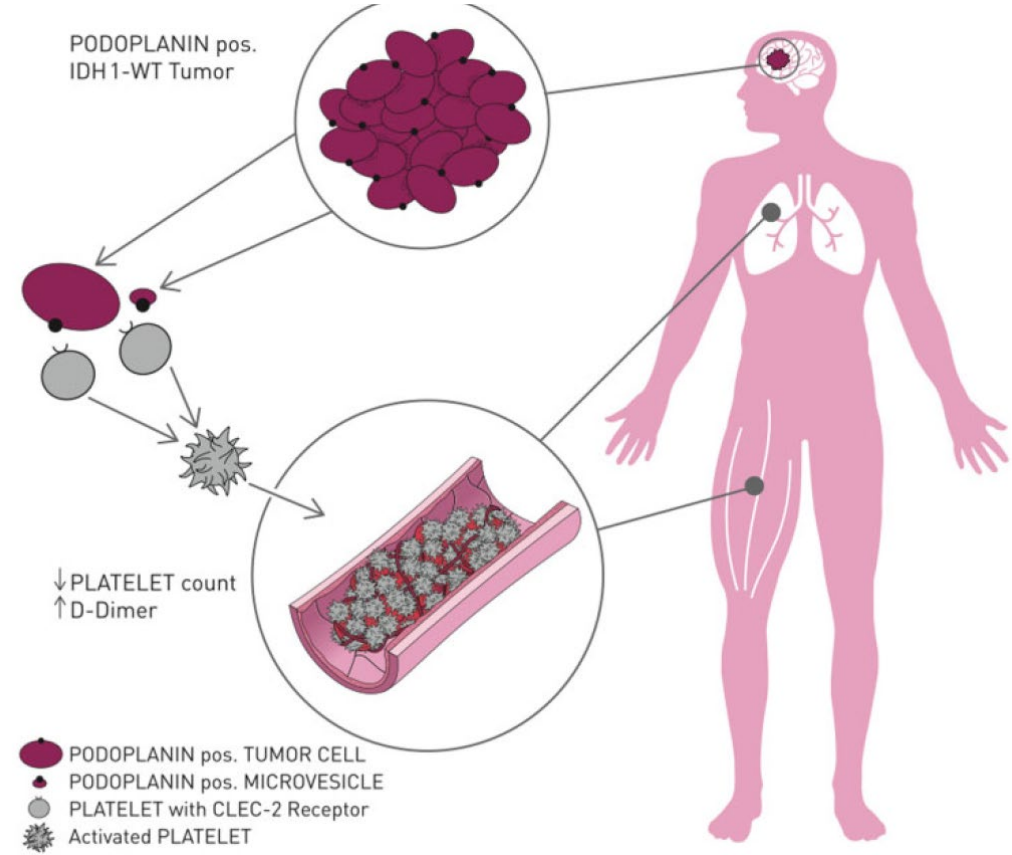
Venous Thromboembolic Disease

- Common
- Among the highest incidence among cancers, comparable to pancreatic and GYN malignancies
- Majority in post-operative period; > 40% outside post-operative period
- Overall risk @ 8% - 30%
  - Perry Neuro-Oncology 2012; Sep;14 Suppl 4:iv73-80
  - Brandes et al Eur J Cancer. 1997;33:1592–1596)
  - Marras et al Cancer. 2000;89:640–646
  - Perry et al. J Thromb Haemost. 2010;8:1959–1965
  - Chinot N Engl J Med 2014;370:709-22

Risk Factors For Venous Thromboembolism in Brain Tumors

Patient-related risk factors	• Older age • Obesity • Dependent functional status (i.e., patients who require assistance from another person for activities of daily living) • Leg paresis
Treatment-related risk factors	• Surgery • Tumor biopsy • Subtotal tumor resection • Use of corticosteroids • Anti-VEGF therapy
Tumor-related risk factors	• Glioblastoma subtype (as compared with lower-grade gliomas) • Intratumoral thrombosis • *IDH1* wild-type status • Podoplanin expression
Laboratory parameters and hemostatic biomarkers	• High white blood cell count • Low platelet count (in contrast to solid tumors) • High soluble P-selectin levels • Elevated coagulation factor VIII activity • Increased D-dimer levels

Abbreviation: IDH1, isocitrate dehydrogenase 1; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism.



Riedl et al. Sem Thrombosis and Hemostasis 20919

Safety of Concurrent Bevacizumab Therapy and Anticoagulation in High-Grade Glioma Patients

Norden et al (J Neurooncol. 2011 Jun 26. [Epub])

- 64/282 HGG treated with bevacizumab and anticoagulation
- 7 (10.9%) were intracranial
  - Grade 4: 2 (3.1%)
  - Grade 1: 5 (7.8%)
- Among 218 patients who did not receive anticoagulants, there were 2 (0.9%) serious hemorrhages (both Grade 4 intracranial hemorrhages)
- Serious hemorrhage rate was higher in patients who received anticoagulants ($p=0.025$), but the rate is low

Lee et al (NEJM 2003; 349:146-153)

- Cancer patients with VTE randomized to coumadin or dalteparin
- After 6 months
  - 27/336 dalteparin had VTE (9%)
  - 53/336 coumadin pt had VTE (17%)
  - (P=0.002)
- No difference in bleeding or death

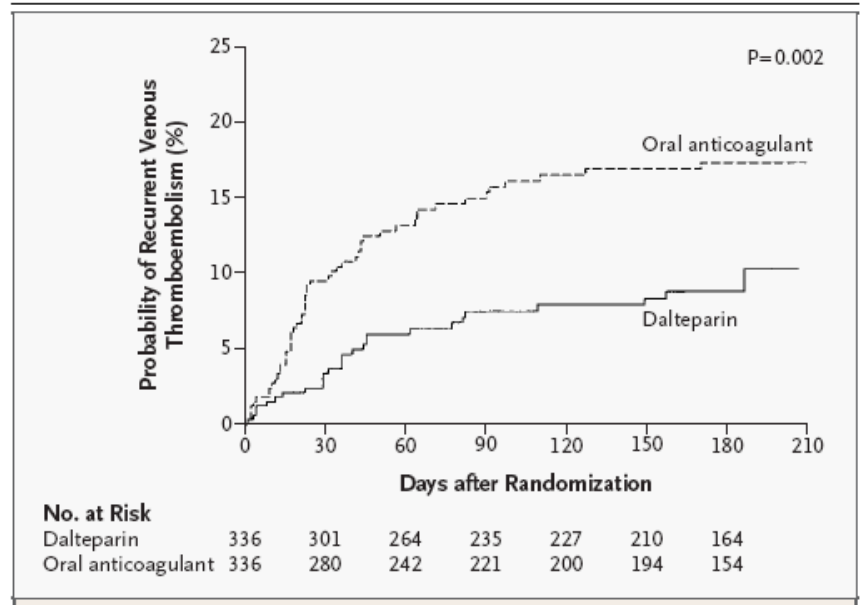


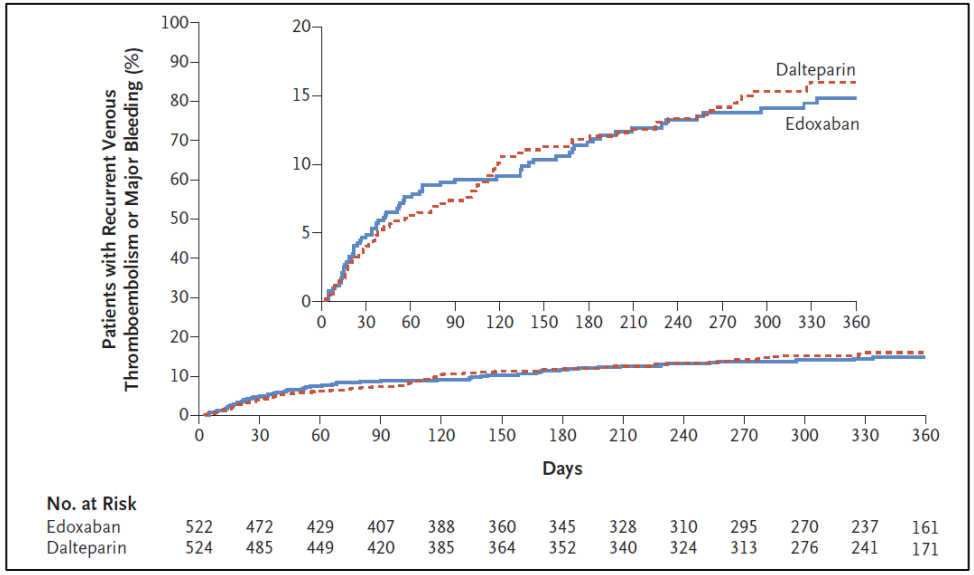
Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

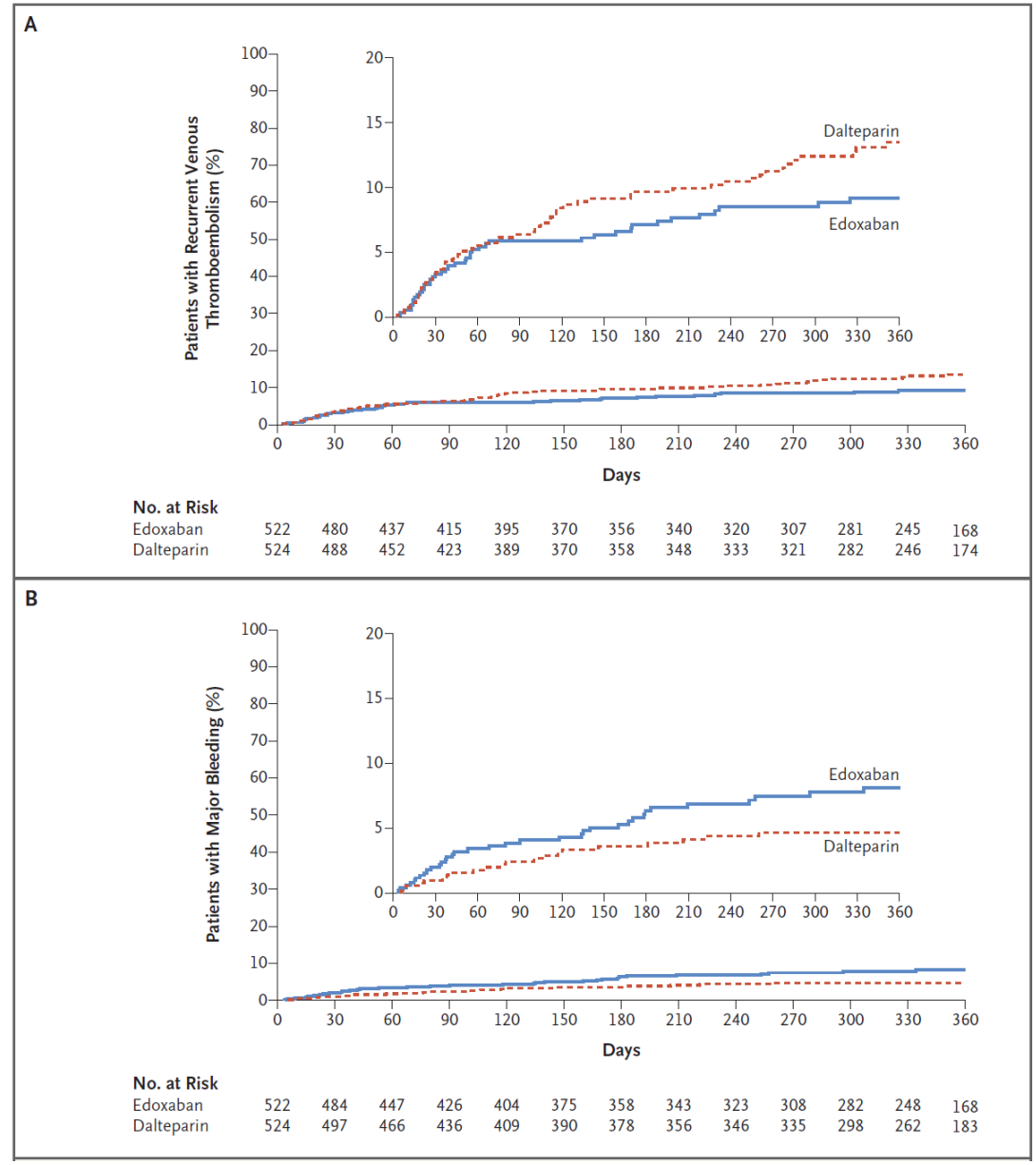
An event was defined as an objectively verified, symptomatic episode of recurrent deep-vein thrombosis, pulmonary embolism, or both during the six-month study period. The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002 by the log-rank test).

The NEW ENGLAND JOURNAL of MEDICINE 2018;378:615

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*





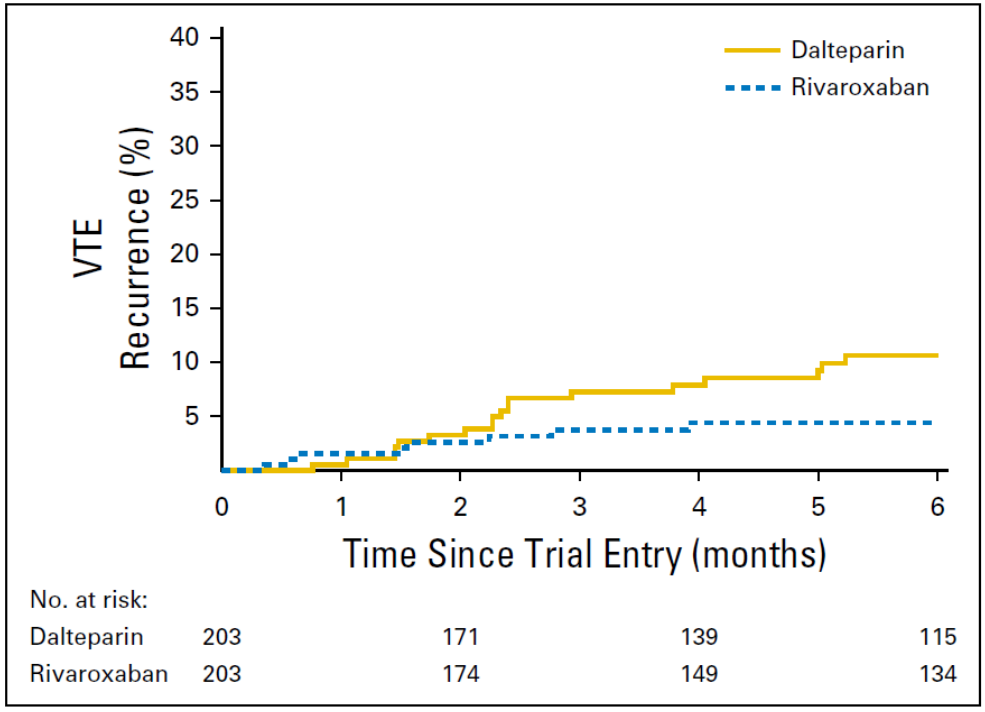


Fig 2. Time to venous thromboembolism (VTE) recurrence within 6 months.

Young et al JCO 2018

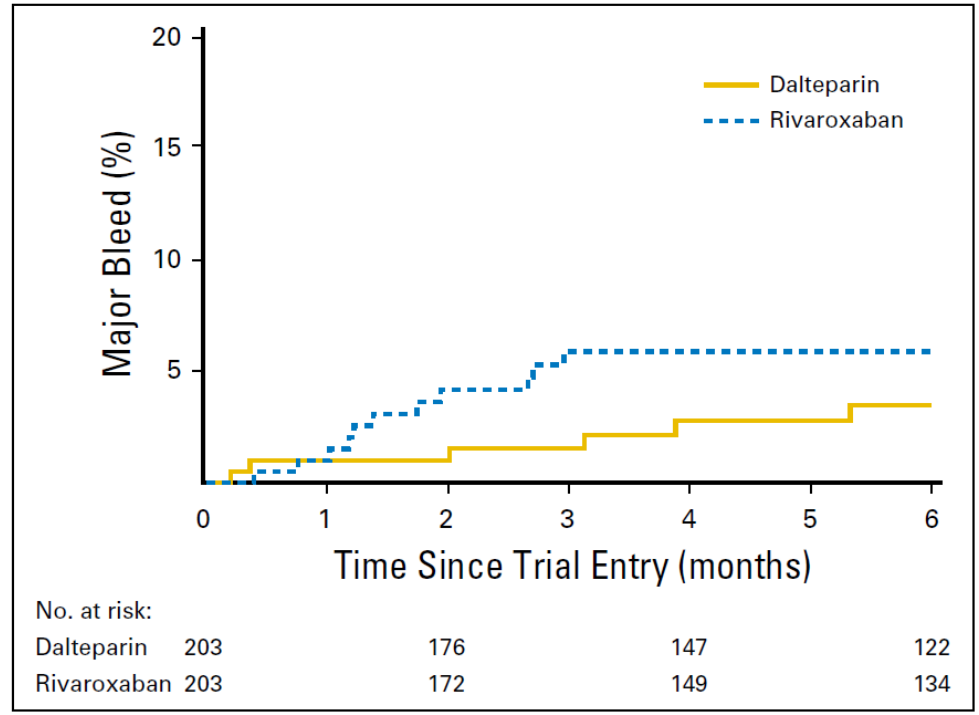


Fig 3. Time to major bleed within 6 months.

Journal of Thrombosis and Haemostasis, 17: 72–76 DOI: 10.1111/jth.14336

ORIGINAL ARTICLE

Intracranial hemorrhage with direct oral anticoagulants in patients with brain tumors

B. J. CARNEY,* E. J. UHLMANN,† M. PULIGANDLA,‡ C. MANTIA,§ G. M. WEBER,¶ D. S. NEUBERG‡ and J. I. ZWICKER*

- Retrospective review of 172 pts (42 DOAC and 131 LMWH)
- Pprimary brain tumor cohort (n = 67), the cumulative incidence of any ICH was 0% in patients receiving DOACs vs. 36.8%(95% confidence interval [CI], 22.3–51.3%) in those treated with LMWH, with a major ICH incidence of 18.2% (95% CI, 8.4–31.0)
- Brain metastases cohort (n = 105), DOACs did not increase the risk of any ICH relative to enoxaparin, with an incidence of 27.8% (95%CI, 5.5–56.7%) compared with 52.9% (95% CI, 37.4–66.2%). Similarly, DOAC did not increase the incidence of major ICH in brain metastases, with a cumulative incidence 11.1% (95% CI, 0.5–40.6%) vs. 17.8% (95% CI, 10.2–27.2%)
- **DOACs are not associated with an increased incidence of ICH relative to LMWH in patients with brain metastases or primary brain tumors**

Recommendations for Patients With VTE

- IVC filter if hemorrhage on CT or other contraindication for anticoagulation
- Heparin initially for sick patients
- LMWH for stable patients
- ? Long term anticoagulation with LMWH preferable for GBM
- ? Role of oral agents such as apixaban (Factor Xa inhibitor)

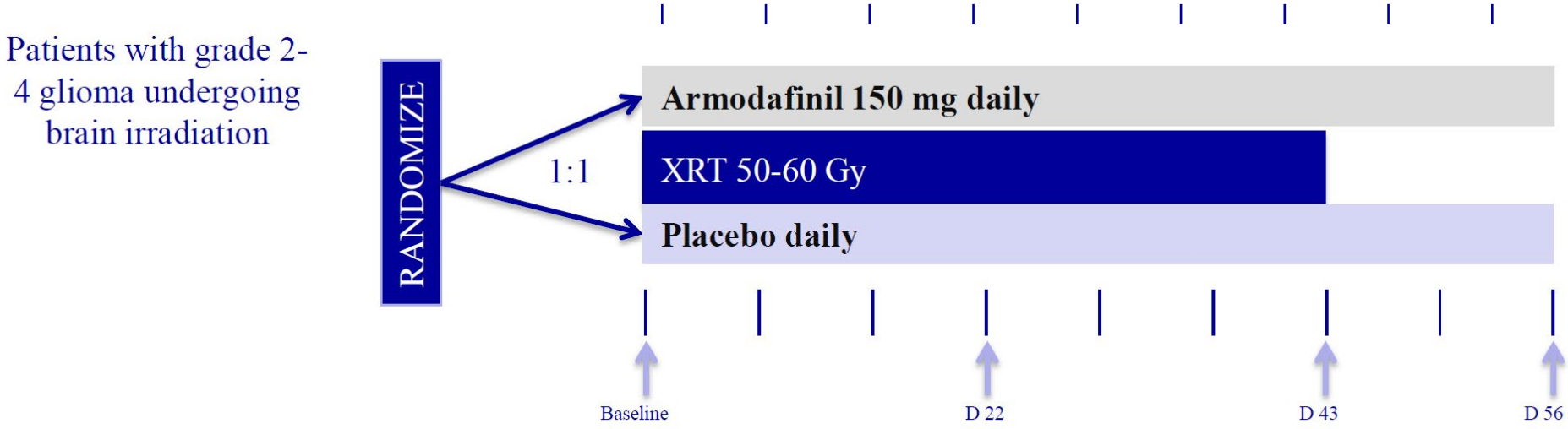
Neuro-Oncology Advance Access published February 21, 2016

Neuro-Oncology

Neuro-Oncology 2016; **0**, 1–6, doi:10.1093/neuonc/now007

A randomized, placebo-controlled pilot trial of armodafinil for fatigue in patients with gliomas undergoing radiotherapy

Eudocia Q. Lee†, Alona Muzikansky†, Jan Drappatz†, Santosh Kesari, Eric T. Wong, Camilo E. Fadul, David A. Reardon, Andrew D. Norden, Lakshmi Nayak, Mikael L. Rinne, Brian M. Alexander, Nils D. Arvold, Lisa Doherty, Jennifer Stefanik, Debra LaFrankie, Sandra F. Ruland, Julee Pulverenti, Katrina H. Smith, Sarah C. Gaffey, Samantha Hammond, and Patrick Y. Wen



- Fatigue assessments with the FACIT-F Fatigue Scale, Brief Fatigue Inventory (BFI), and Cancer Fatigue Scale (CFS) at baseline, day 22, day 43, and day 56.
- PRIMARY ENDPOINT: Difference in the 42-day change in FACIT-F fatigue subscale scores between armodafinil group vs. placebo group
- SECONDARY ENDPOINTS: 42-day change in CFS and BFI, safety

VOLUME 33 · NUMBER 15 · MAY 20 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Donepezil for Irradiated Brain Tumor Survivors: A Phase III Randomized Placebo-Controlled Clinical Trial

Stephen R. Rapp, L. Doug Case, Ann Peiffer, Michelle M. Naughton, Michael D. Chan, Volker W. Stieber, Dennis F. Moore Jr, Steven C. Falchuk, James V. Piephoff, William J. Edenfield, Jeffrey K. Giguere, Monica E. Loghin, and Edward G. Shaw

- **198 adult brain tumor survivors 6 months after partial- or whole-brain irradiation** randomly assigned to receive a single daily dose (5 mg for 6 weeks, 10 mg for 18 weeks) of donepezil or placebo
- Cognitive test battery assessing memory, attention, language, visuomotor, verbal fluency, and executive functions was administered before random assignment and at 12 and 24 weeks. A cognitive composite score (primary outcome) and individual cognitive domains were evaluated

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- After 24 weeks of treatment, the composite scores did not differ significantly between groups (*P* .48)
- Modest improvements in several cognitive functions, especially among patients who were more cognitively impaired
- Significant differences favoring donepezil were observed for memory (recognition, *P* .027; discrimination, *P* .007) and motor speed and dexterity (*P* .016)

Minimizing neurocognitive decline from WBRT?

- **RTOG 0614:** phase III randomized, placebo-controlled study
- Placebo vs. Memantine 20 mg daily within 3 days of starting WBRT 37.5 Gy and continued for 24 weeks

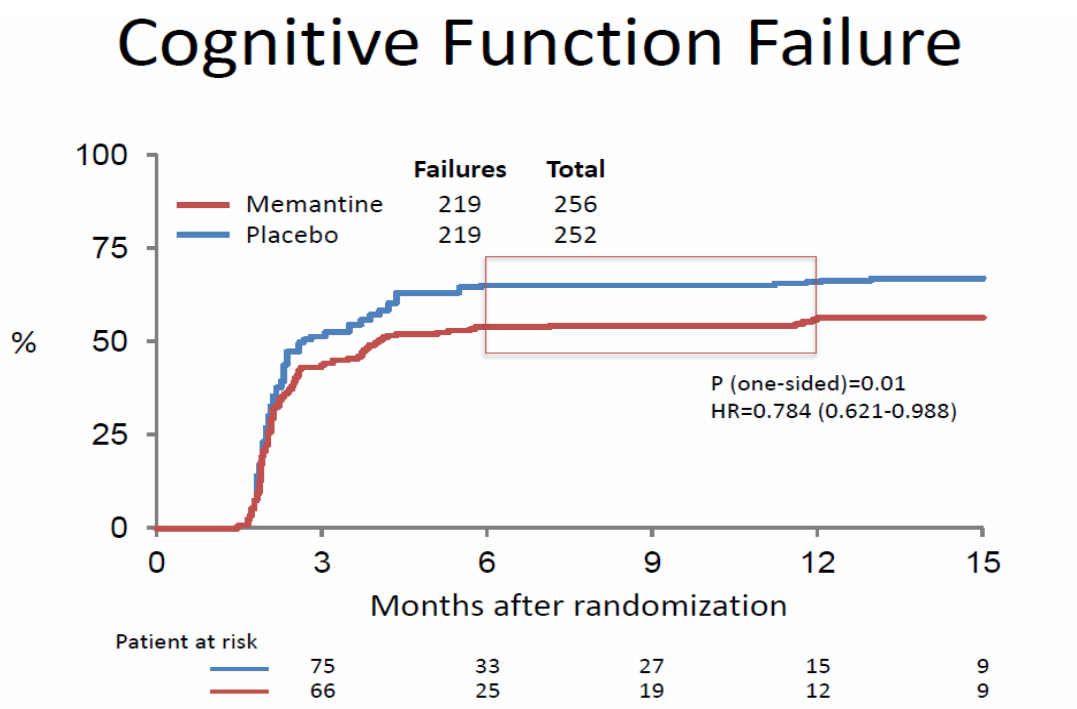
Cognitive domain	Measure
Memory	Hopkins Verbal Learning Test-Revised
Processing speed	Trail making test Part A
Executive function	Trail making test Part B, controlled oral word association
Global function	Mini-mental status examination
Cognitive function (self-report)	Medical outcomes scale – cognitive function scale
Quality of life	Fact-Br

MRI, Cognitive Assessment and QOL at Baseline, 8, 16, 24 and 52 weeks

Laack NNI, et al. RTOG 0614. Presented at ASTRO 2012.
Brown PD, et al. Int J Rad Oncol Biol Phys 2012; 84 (3S): S1-S2

Outcomes: RTOG 0614

- Primary endpoint: Reduced the decline in HVLT-R DR by 0.9 **(P=.059)** at 24 weeks



- 17% reduced relative risk of cognitive decline **(p=.01)**
- Delayed time to cognitive decline **(p=.01)**
- Reduced the rate of decline in cognitive, executive, and global function as well as processing speed **(p<.01)**

Laack NNI, et al. RTOG 0614. Presented at ASTRO 2012

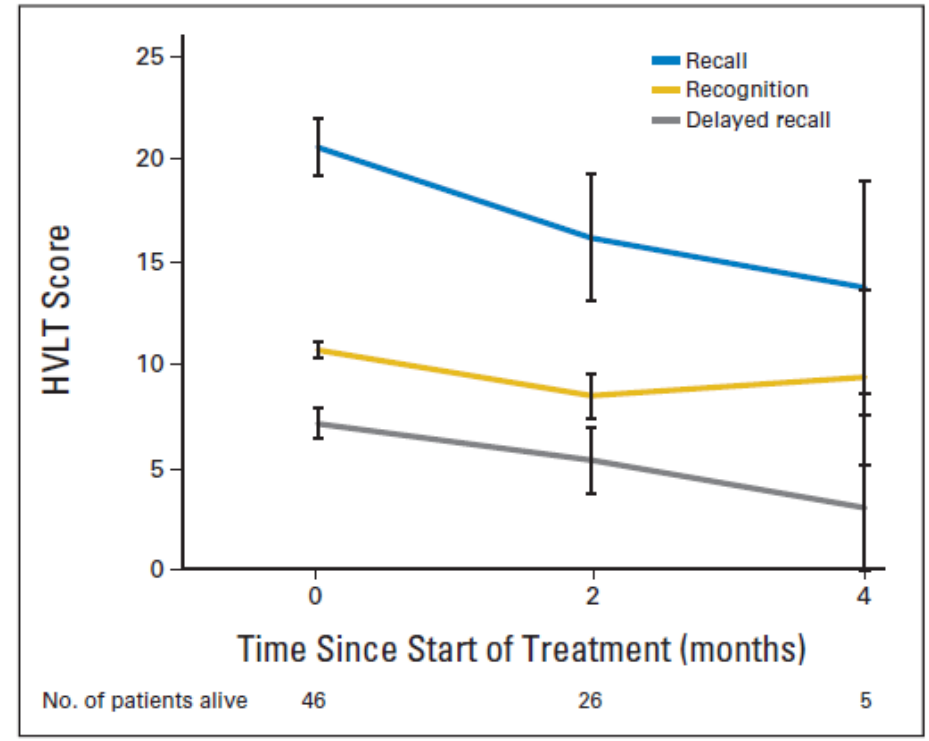
VOLUME 32 · NUMBER 34 · DECEMBER 1 2014

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

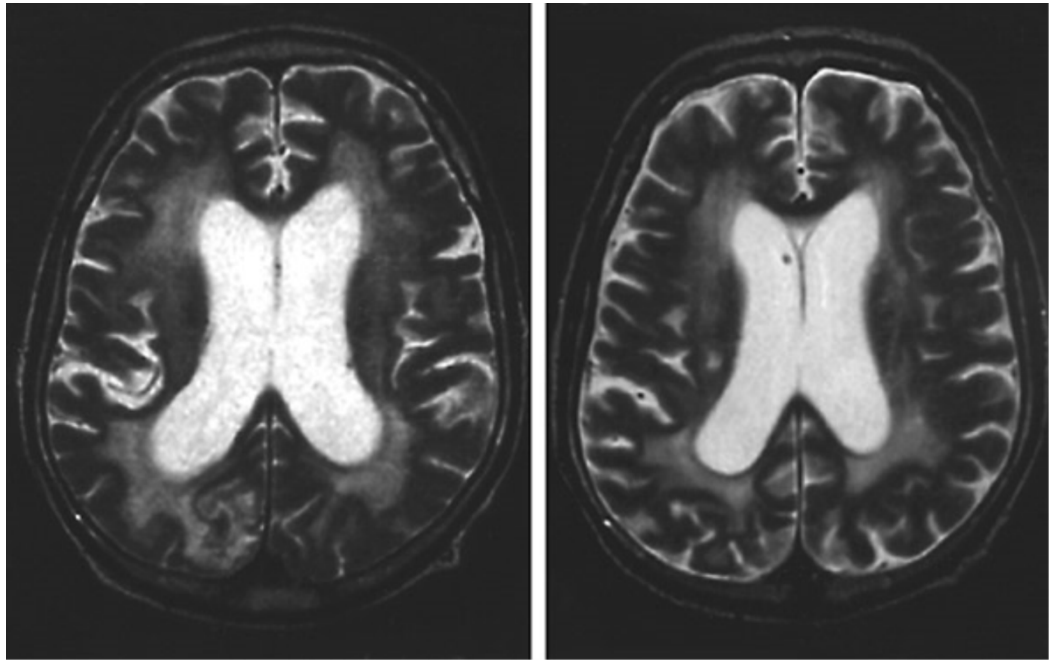
Preservation of Memory With Conformal Avoidance of the Hippocampal Neural Stem-Cell Compartment During Whole-Brain Radiotherapy for Brain Metastases (RTOG 0933): A Phase II Multi-Institutional Trial

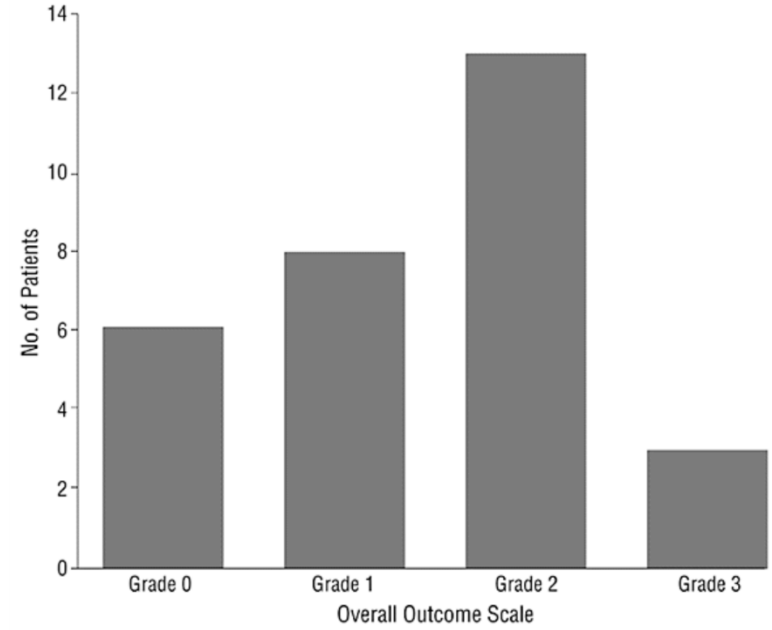
Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tome, Chip Caine, Ben Corn, Andrew Kanner, Howard Rowley, Vijayananda Kundapur, Albert DeNittis, Jeffrey N. Greenspoon, Andre A. Konski, Glenn S. Bauman, Sunjay Shah, Wenyin Shi, Merideth Wendland, Lisa Kachnic, and Minesh P. Mehta

- Patients with brain metastases received HA-WBRT to 30 Gy in 10 fractions.
- Standardized cognitive function and quality-of-life (QOL) assessments were performed
- 113 patients accrued, 42 patients were analyzable at 4 months
- Mean relative decline in HVLT-R DR from baseline to 4 months was 7.0% (95% CI, 4.7% to 18.7%), significantly lower in comparison with the historical control (P 0.001). No decline in QOL scores was observed.
- Conformal avoidance of the hippocampus during WBRT is associated with preservation of memory and QOL compared with historical series.



Hydrocephalus in Radiation Leukoencephalopathy: Results of Ventriculoperitoneal Shunting





Grade 0 indicates no improvement; grade 1, mild improvement; grade 2, moderate improvement; and grade 3, marked improvement.

Thiessen et al. *Arch Neurol.* 1998;55(5):705-710

VOLUME 29 · NUMBER 21 · JULY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Exercise Behavior, Functional Capacity, and Survival in Adults With Malignant Recurrent Glioma

Emily Ruden, David A. Reardon, April D. Coan, James E. Herndon II, Whitney E. Hornsby, Miranda West, Diane R. Fels, Annick Desjardins, James J. Vredenburgh, Emily Waner, Allan H. Friedman, Henry S. Friedman, Katherine B. Peters, and Lee W. Jones

Conclusion

Exercise behavior is a strong independent predictor of survival that provides incremental prognostic value to KPS as well as traditional markers of prognosis in malignant recurrent glioma.

VOLUME 27 · NUMBER 7 · MARCH 1 2009

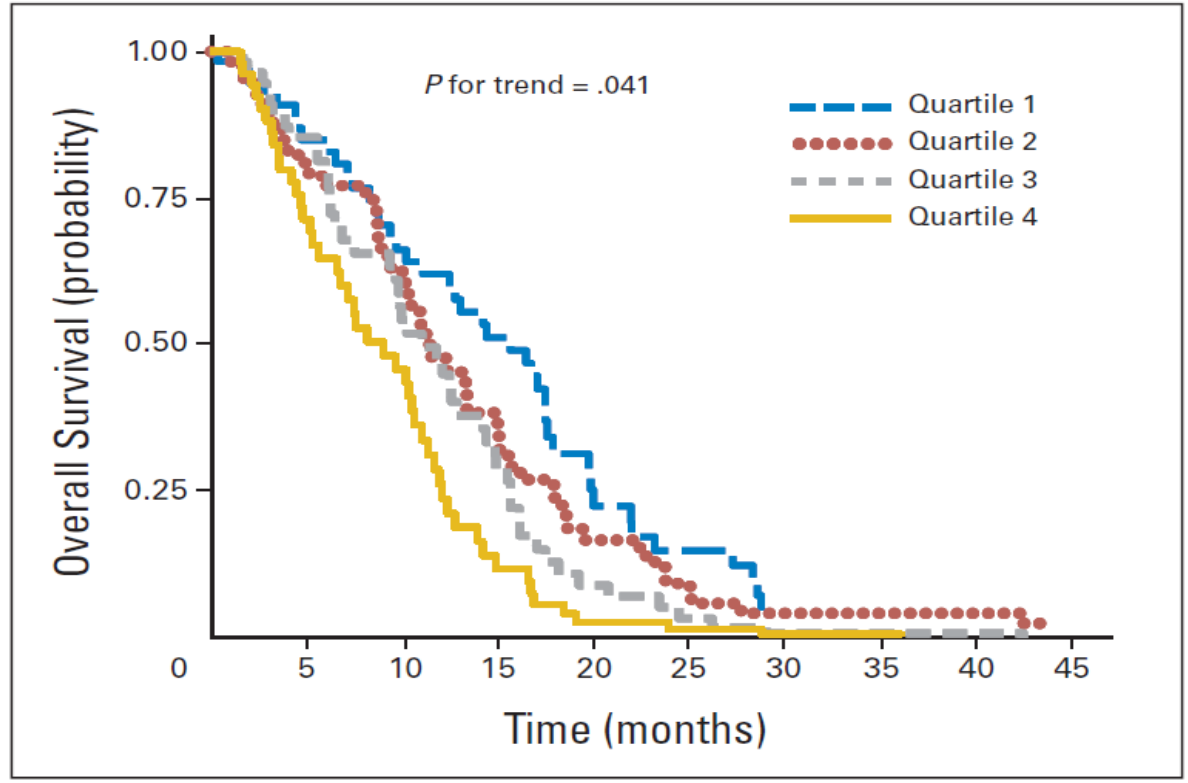
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Association Between Hyperglycemia and Survival in Patients With Newly Diagnosed Glioblastoma

Rachel L. Derr, Xiaobu Ye, Melissa U. Islas, Serena Desideri, Christopher D. Saudek, and Stuart A. Grossman

- 191 newly diagnosed GBM patients
- Hyperglycemia associated with shorter survival, after controlling for glucocorticoid dose and other confounders
- Effect of intensive management of glucocorticoid-related hyperglycemia on survival deserves additional study



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