Breast Cancer: Brain Mets

Thank you:

Susan Komen Foundation

NIH-NCI

RTOG

All Participants

Why Are We Here? Long-term Goals

- Determine the population at risk
- Develop preventive strategies
- Is there a role for surveillance?
- Develop effective therapies
- Understand the biology better

Why Are We Here? Immediate Goals

- We need one or more trials for patients with Her2+ Ca and brain mets.
- We need to refine our end-points, e.g. neurological PFS.
- XRT is the current standard of care for these patients, who offer opportunities for testing combinations of XRT + targeted agents.
  - There is particularly strong interest in triple-negative cancer because DNA-repair pathways are perturbed and offers attractive targets.

Meeting Structure

- Please respect your time & allow for Qs.
- Edit your slides to eliminate repetition.
- D1: 9 speakers: overview; preclinical data; lessons from completed trials; targeted agents.
- D2: 11 speakers: clinical trial designs & resources; imaging; surgery; radiosurgery; PCI; surrogate endpoints; cognition.
- D2: Roundtable & ? Publication.

Motexafin Gadolinium Trial (9801) Lessons Learned

Minesh Mehta, MD, University of Wisconsin

COI: None at the time of the trial & publication; as of 2009, PCYC Board Member

Lessons Learned

- It is difficult, but possible to do large randomized brain met trials, but it requires a very motivated organization
- In terms of clinical history, breast cancer patients are very different from NSCLC
- In terms of survival, breast cancer patients are not all that different from NSCLC
- Neurologic and cognitive endpoints can be tested and are relevant

Lessons Learned

- Neurologic and cognitive endpoints are not readily acceptable to the FDA: *discussion*
- Centralized imaging and volumetric assessment is very feasible, but expensive
- Individual lesions display considerable response heterogenity

Study Design

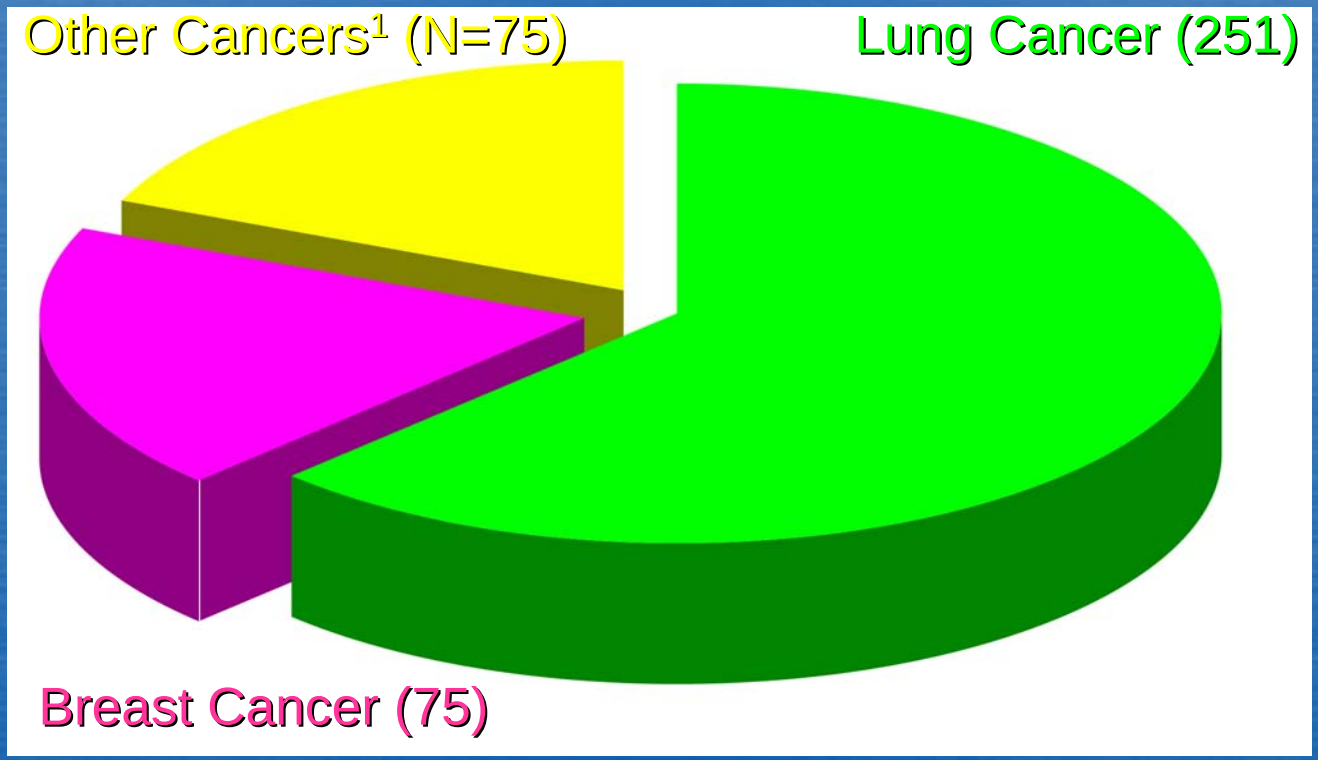
- International, randomized phase III trial
  - XRT alone (30 Gy/10 fx) vs.
  - XRT plus MGd, 10 doses (5 mg/kg, IV)
- Stratification by
  - Tumor type (Lung/breast/others)
  - Recursive Partitioning Analysis Class (1 vs 2)
  - Study center
- Co-Primary endpoints:
  - Survival
  - Time to Neurologic Progression
- Secondary endpoints
  - Neurocognitive progression
  - Loss of functional independence
  - Radiologic response and progression

Assessments

- Neurocognitive testing: monthly x 6, then q 3 mo
  - Hopkins Verbal Learning Test (HVLT)
  - Controlled Oral Word Association (COWA)
  - Trailmaking Tests A & B
  - Grooved Pegboard
- Neurologic symptoms: monthly x 6, then q 3 mo
- Neurologic exam: monthly x 6, then q 3 mo
- Barthel Index: monthly x 6, then q 3 mo
- Neurologic progression: monthly x 6, then q 3 mo
- FACT-BR: monthly x 6, then q 3 mo
- MRI: 0. 2, 4 and 6 months, then q 3 mo

Enrollment by Primary Cancer

N=401 (208 Control, 193 MGd)



[1] Other tumors were melanoma (24), primary of unknown origin (11), renal (11), colorectal (7), esophageal (7), bladder (3), ovarian (3), thyroid (2), sarcoma (2), gastric (1), pancreatic (1), ureteral (1), endometrial (1), and prostate cancer (1)

Lung Cancer Patients Differ from Breast Cancers

Lung accrual = x3 breast accrual

	Lung n=251	Breast n=75	Other n=75
Presenting with brain metastases (%)	46.6	2.7	28.0
Brain only site of metastasis (%)	61.4	22.7	43.2
≥2 extracranial organs with metastatic involvement (%)	0.0	38.7	2.7
Median sum of indicator lesion volume (mL)	7.0	11.0	15.0
Median time, primary cancer D_x to brain met R_x (months)	3.8	38.3	12.5
Median number of prior chemotherapy cycles	0.0	9.0	0.0

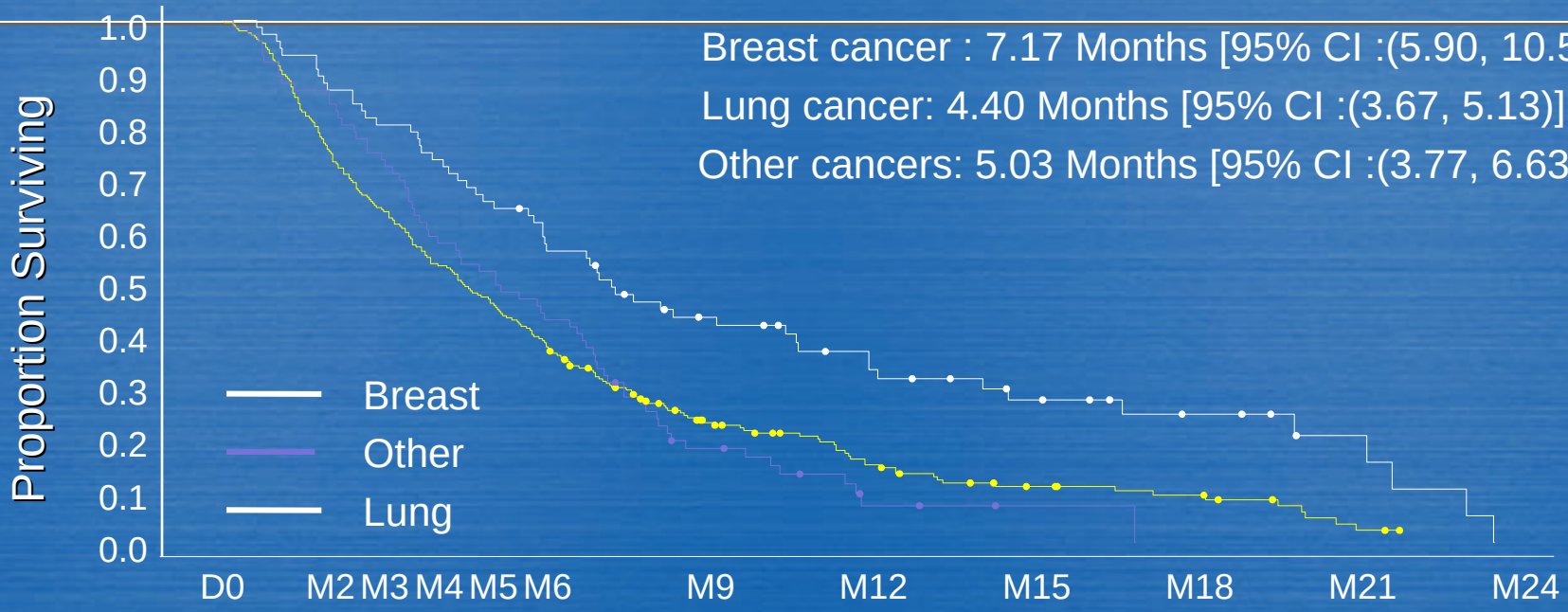
Breast Patients Have Slightly Better Survival

Median Survival

Breast cancer : 7.17 Months [95% CI :(5.90, 10.57)]

Lung cancer: 4.40 Months [95% CI :(3.67, 5.13)]

Other cancers: 5.03 Months [95% CI :(3.77, 6.63)]



Time Since Randomization

Sample size

Lung	251	188	159	133	115	94	47	27	15	11	2	0
Breast	75	65	60	55	49	41	28	19	13	8	4	0
Other	75	63	55	43	39	32	12	3	1	0	0	0

Neurocognitive Function and Progression in Patients With Brain Metastases Treated With Whole-Brain Radiation and Motexafin Gadolinium: Results of a Randomized Phase III Trial

Christina A. Meyers, Jennifer A. Smith, Andrea Bezjak, Minesh P. Mehta, James Liebmann, Tim Illidge, Ian Kunkler, Jean-Michel Caudrelier, Peter D. Eisenberg, Jacobus Meerwaldt, Ross Siemers, Christian Carrie, Laurie E. Gaspar, Walter Curran, See-Chun Phan, Richard A. Miller, and Markus F. Renschler

Table 6. Significant Multivariate Predictors of Survival

Factor at Baseline	*P*
Sex	< .0001
Brain metastases, 1-2 *v* > 2	.0001
KPS, 70–80 *v* 90–100	.0044
High serum LDH	< .0001
Low serum LDH	.0292
Low serum albumin	.0014
Breast cancer	.0071
Time from diagnosis to enrollment	.0344
Motor speed and dexterity, pegboard dominant hand	.0233

NOTE. Multivariate analysis of clinical data and neurocognitive tests by multivariate Cox models.
Abbreviations: KPS, Karnofsky performance score; LDH, lactate dehydrogenase.

Murray, et al; first showed the impact of baseline MMSE on survival Significant factors for survival were pretreatment MMSE (p = 0.0002), and KPS (p = 0.02). RTOG 9104, n = 445

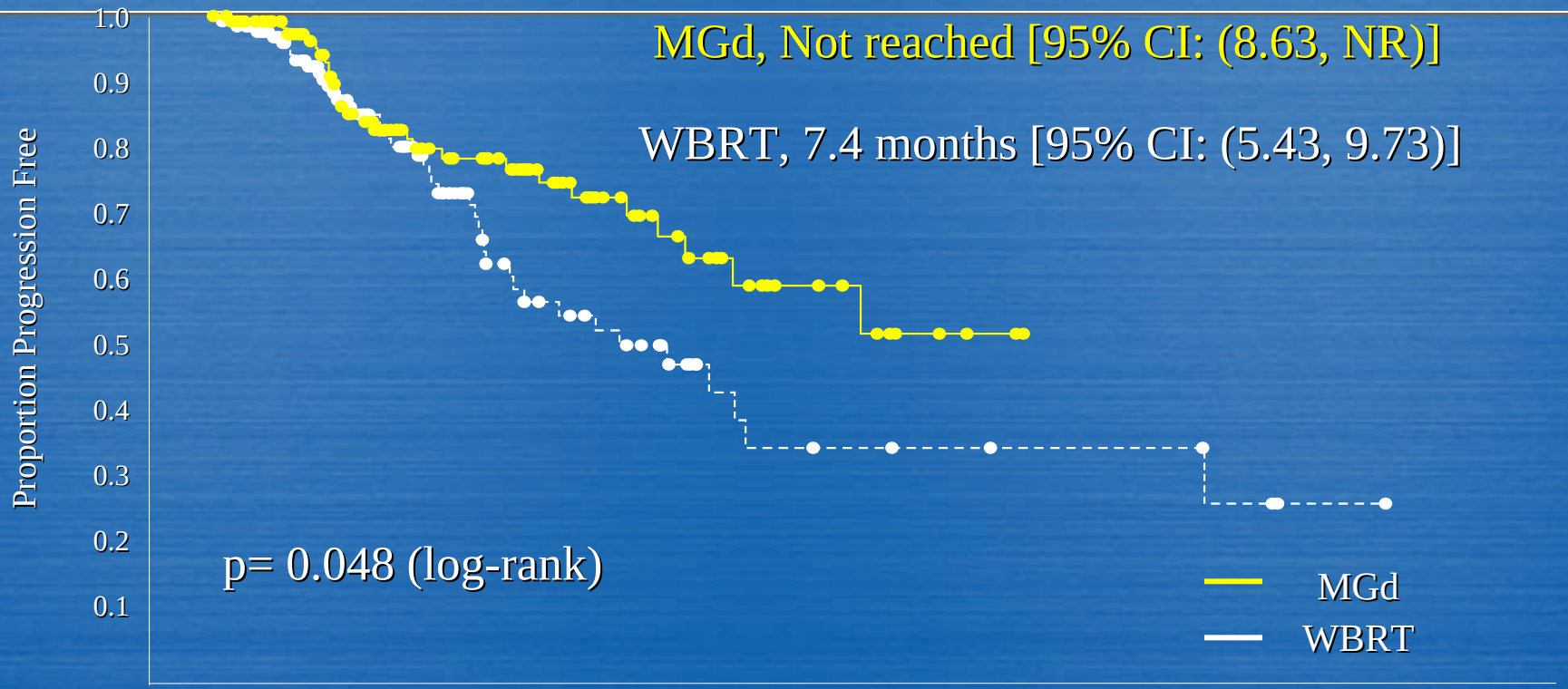
Meyers C, et al, JCO 22: Jan 2004; Murray, et al, 48: 2000, IJROBP,

Time to Neurologic Progression: Lung Cancer (By Events Review Committee): Feasibility Demonstrated

Median Time to Neurologic Progression

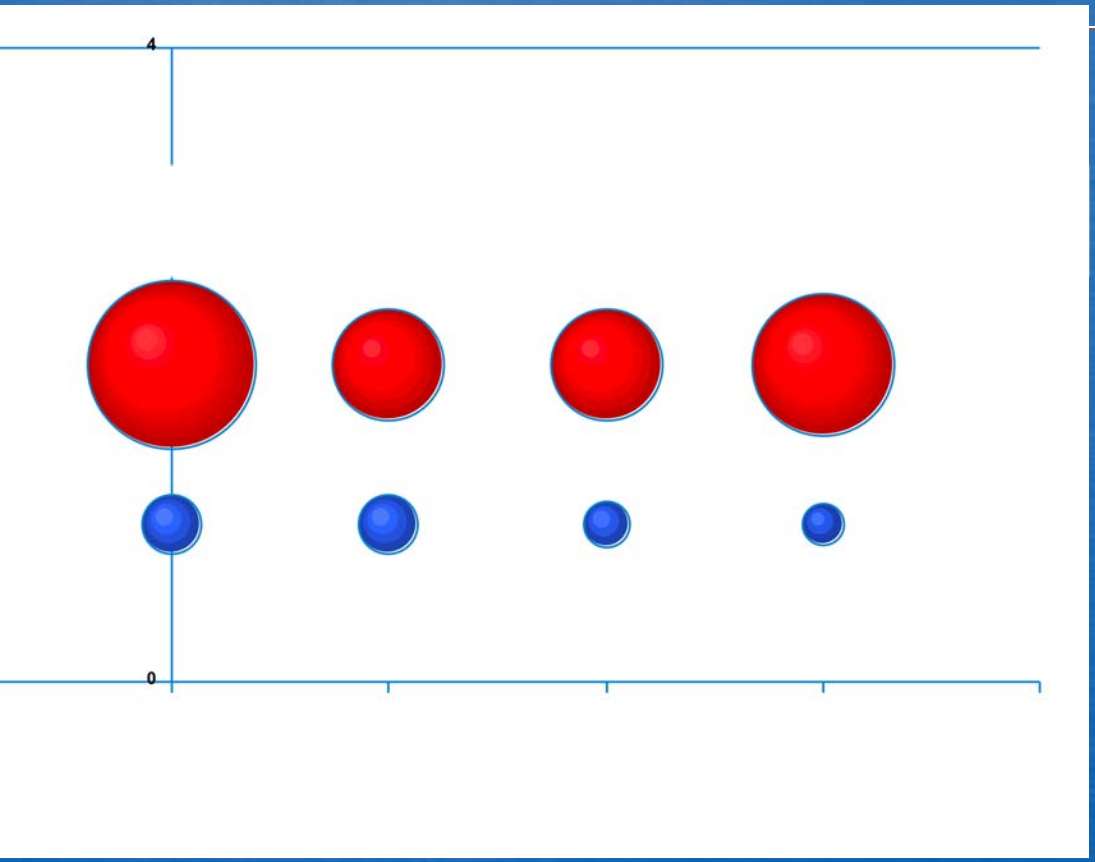
MGd, Not reached [95% CI: (8.63, NR)]

WBRT, 7.4 months [95% CI: (5.43, 9.73)]



Sample size	D0	D28	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24
MGd	123	113	88	66	53	49	37	18	7	0	0	0	
WBRT	128	119	91	71	53	35	27	11	7	5	5	1	

Interlesional Response Variability



247 brain mets: 30 Gy/10fx

MR Tumor volume over 4 mo

Maximum likelihood variance component analysis:

Between patients: 57%

Between lesions: 43%

Bentzen, Li, Mehta (submitted)

Lessons Learned

- It is difficult, but possible to do large randomized brain met trials, but it requires a very motivated organization
- In terms of clinical history, breast cancer patients are very different from NSCLC
- In terms of survival, breast cancer patients are not all that different from NSCLC
- Neurologic and cognitive endpoints can be tested and are relevant: *tomorrow*

Lessons Learned

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- Centralized imaging and volumetric assessment is very feasible, but expensive
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Cognitive Evaluation & Neuroprotective Strategies

Minesh Mehta, MD, University of Wisconsin

Oncologists Treat Brain Metastases to Improve Neurologic Function

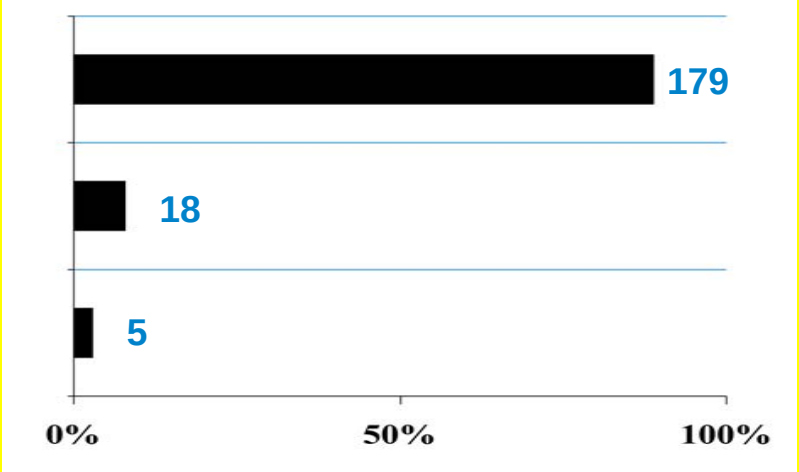
Results of a Physician Survey (N=202)

Improve Neurologic/Neurocog Function and QOL

Improve Survival Only

Improve Survival & Neurologic/Neurocognitive/QOL

Treatment Goals



Delaying WBRT, with increased brain failure (rapidly), is associated with non-salvagable neurocognitive decline:

This is not consonant with treatment objectives

Renschler, MF et al Proc ASCO 2003 **Responses from Market Research conducted by McKesson Health at ASCO 2001 (N=92) and ASTRO (N=110) with Medical and Radiation Oncologists**

Neurocognitive Tests Completion Rates

Myth: Brain met patients have low compliance with neurocog testing

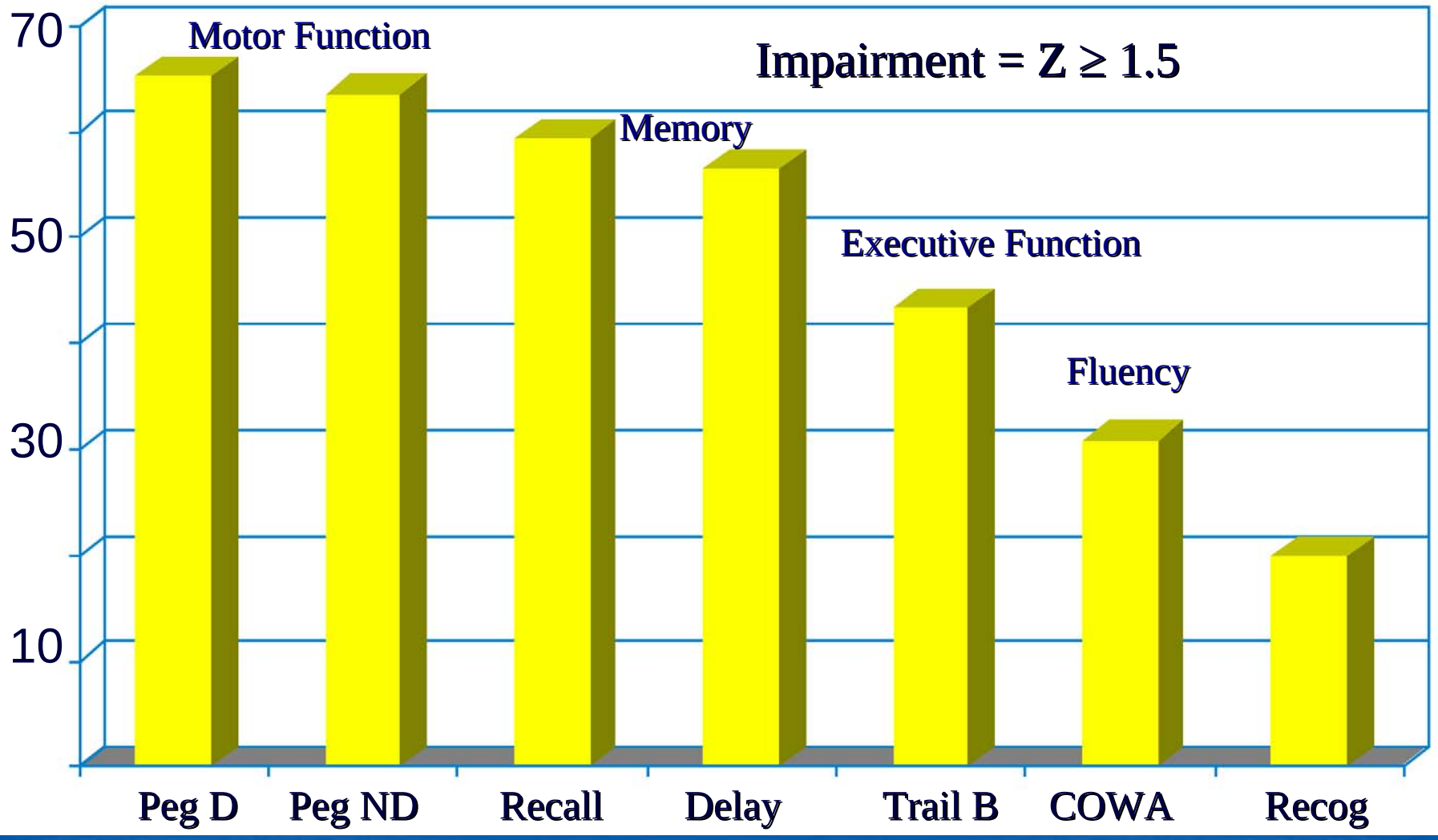
	Months After Randomization											Total	Total
	0	1	2	3	4	5	6	9	12	15	18	N	%
Patient Visits	401	327	269	205	178	138	127	66	33	23	13	1783	100
HVLT Recall Completed (%)*	98	90	86	83	84	81	87	89	85	78	62	1577	88
Trail B Completed (%)^	87	82	75	74	74	72	77	86	76	78	62	1409	79

Fact: Brain met patients have high compliance with neurocog testing

* Highest and ^ lowest completion tests

Many Patients Are Impaired at Presentation

Fact: Brain met patients have high rates of baseline neurocog deficits



Neurocognitive Function Correlates with Indicator Lesion Volume at Presentation

	Memory Recall	Memory Recog	Memory Delayed Recall	Verbal Fluency COWA	Pegboard: Dominant Hand	Pegboard: Non-Dominant Hand	Exec Function Trail B
r[1]	0.211	0.147	0.207	0.187	0.221	0.237	0.086
P	0.0001	0.0036	0.0001	0.0001	0.0001	0.0001	0.0001
N	390	392	370	388	370	361	346

[1]Spearman correlation coefficients for sum of indicator lesion volume and z-scores of neurologic tests

Impaired Neurocognitive Function is Associated with Poor Quality of Life

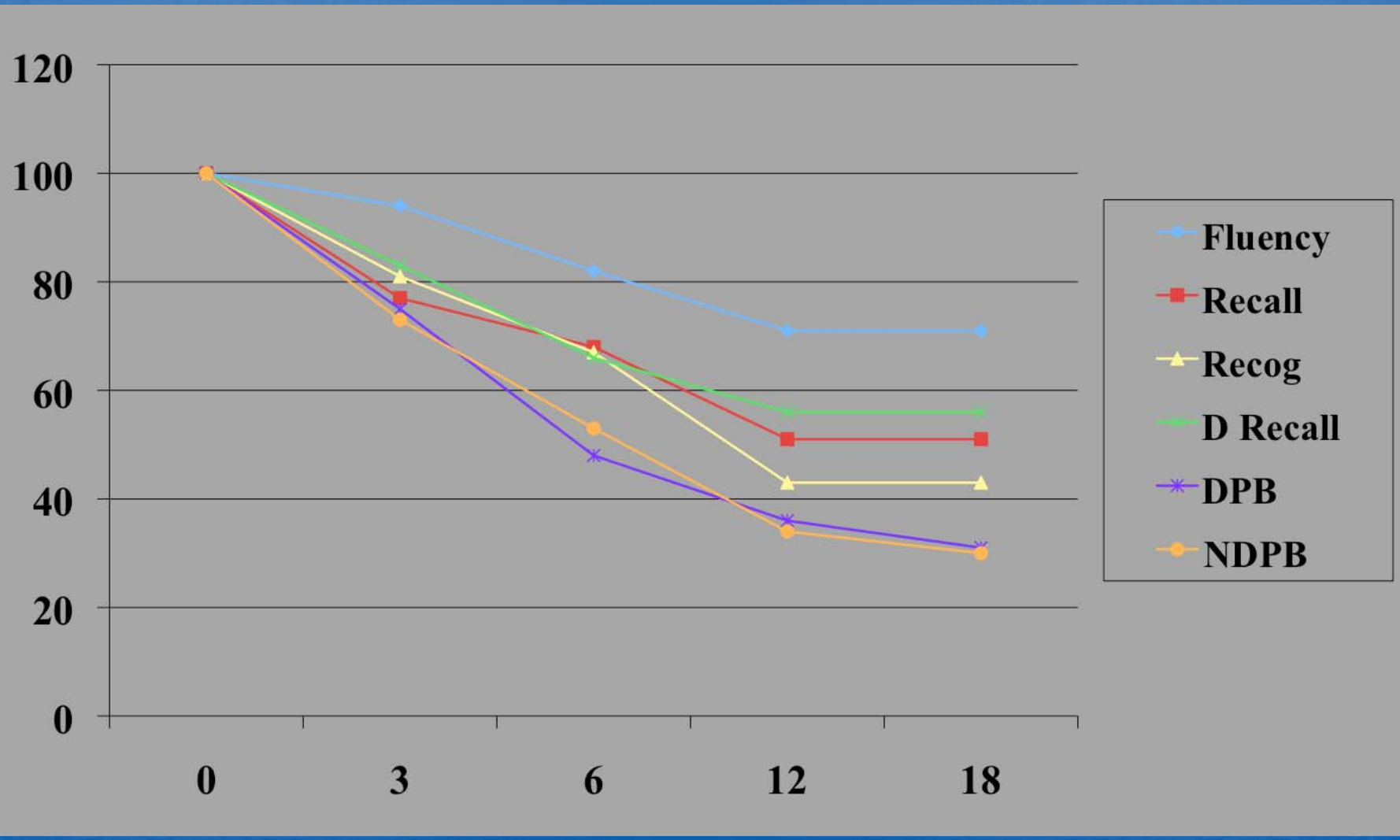
Mean QOL score as a function of degree of neurocognitive impairment

#Impaired	FACT-BR	FACT-G	BR	TOI[2]	PWB	SWB	EWB	FWB
≤ 3 Tests	133.0	77.9	55.0	93.6	21.6	23.1	16.3	16.9
> 3 Tests	121.9	73.6	48.2	83.7	20.6	22.4	15.8	14.9
P-value[1]	0.0001	0.0018	0.0001	0.0001	0.0468	0.1334	0.275	0.0003

[1]T-test comparing QOL score in patients with high or low neurocognitive impairment

[2]Treatment Outcome Index (Physical and Functional Well-Being, Brain-Related Additional Concerns)

WBRT: Neurocog time course



208 patients on WBRT alone arm, PCYC Ph III trial

Tumor Remission at Different Time Points

Months	2	4	6	9	12	15
% pts with CR	4.6	5.9	13	15	35	21
% pts with PR	25	33	29	27	35	50
% pts with remission	30	38	41	42	71	71
# of pts	131	85	55	33	17	14

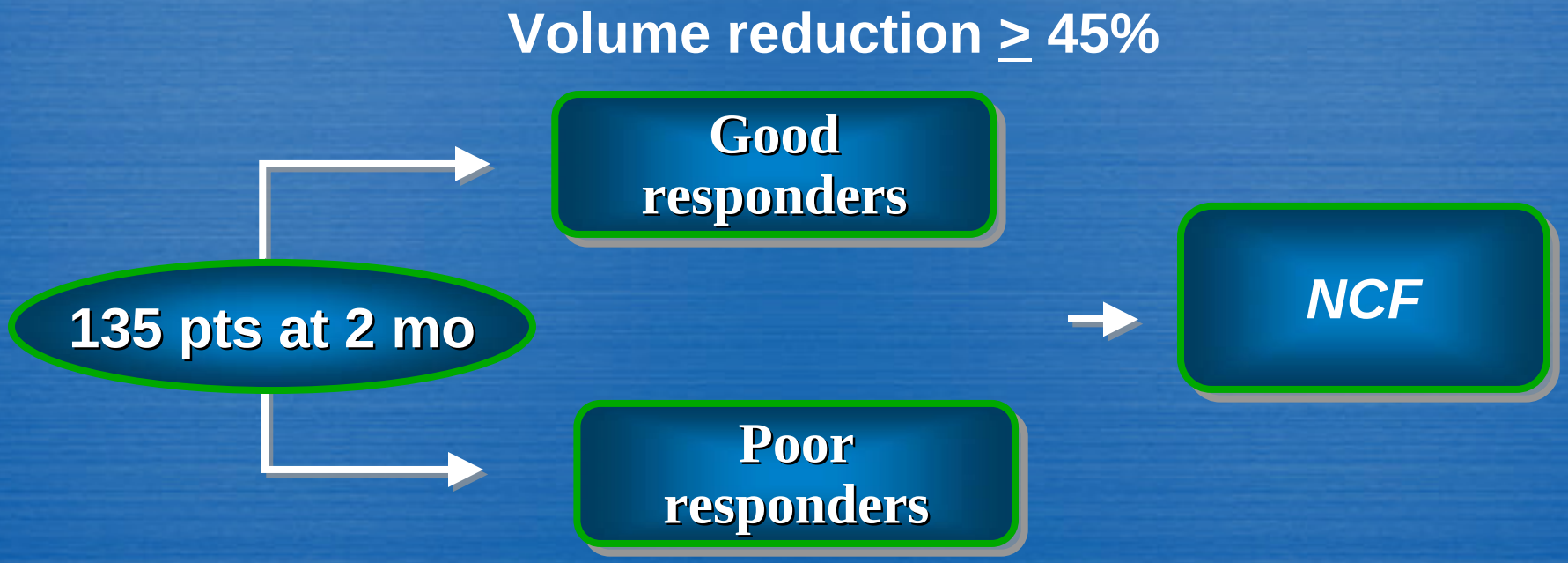
Relationship b/t NCF and Tumor Volume Reduction

- **Goal - Correlate changes in NCF and MRI-measured tumor volume following WBRT in BM pts**

- **Approaches**
  - **Do Pts with greater tumor volume reduction have slower progression of NCF?**
    - **Subgroup analysis**
  - **Are tumor reduction and NCF deterioration correlated?**
    - **Spearman's rank correlation in long-term survivors**
  - **What is the time course of NCF and tumor volume?**
    - **Mean NCF and tumor volume in long vs short-term survivors**

Grouping of Pts Based on Tumor Volume Reduction

Median tumor volume reduction at 2 mo: 45%



Median Time to NCF Deterioration

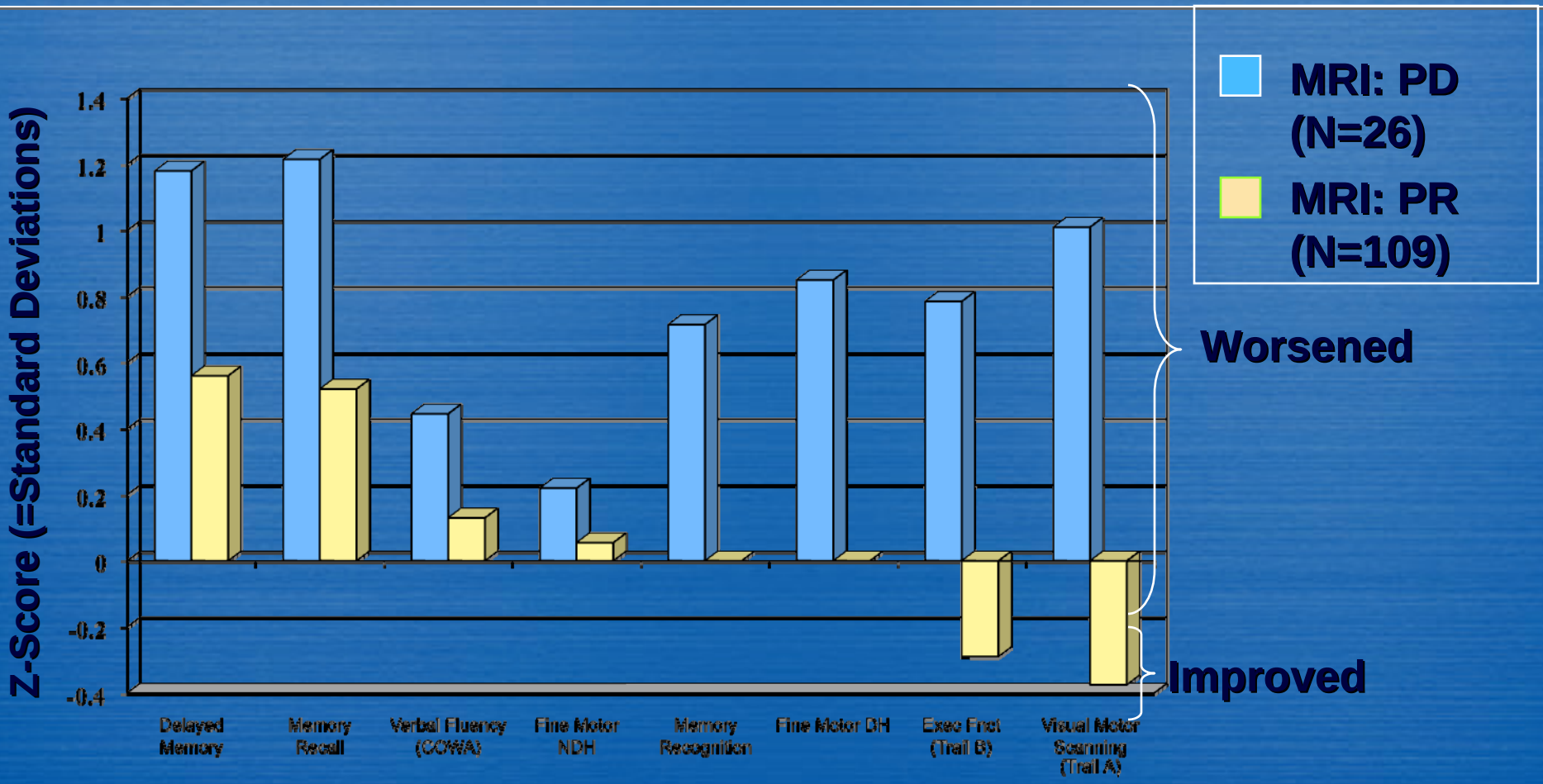
Median time to NCF decline (days)	Memory Recall	Memory Recognition	Memory Delayed Recall	Verbal Fluency: COWA	Pegboard DH	Pegboard NDH	Executive Function: Trail A	Executive Function: Trail B
Good responders	416	374	431	512	380	401	391	462
Poor responders	355	322	372	441	287	291	386	331
Net gain (days)	61	52	59	71	93	110	5	131
P values	0.205	0.478	0.315	0.243	0.049	0.021	0.237	0.017
No of Pts	131	131	131	131	132	132	132	131

NCF deterioration: ≥ 2 SD from baseline on 2 consecutive measurements or on the last follow-up visit before death

**** All values in yellow are statistically significant***

Tumor Growth Correlates with Neurocognitive Decline

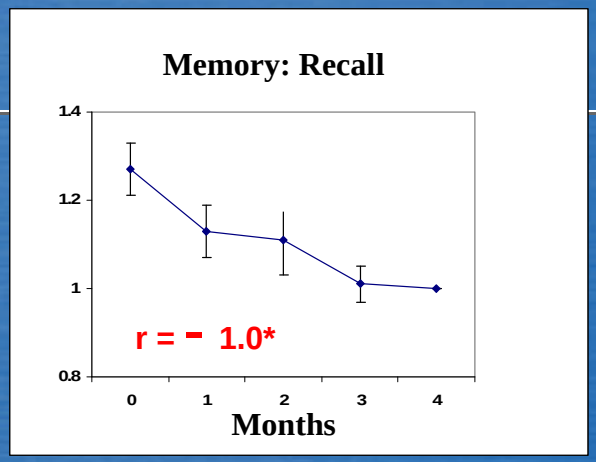
Median Change in Neurocognitive Test Performance (Z-score) at 4 Months in Patients with MRI Data

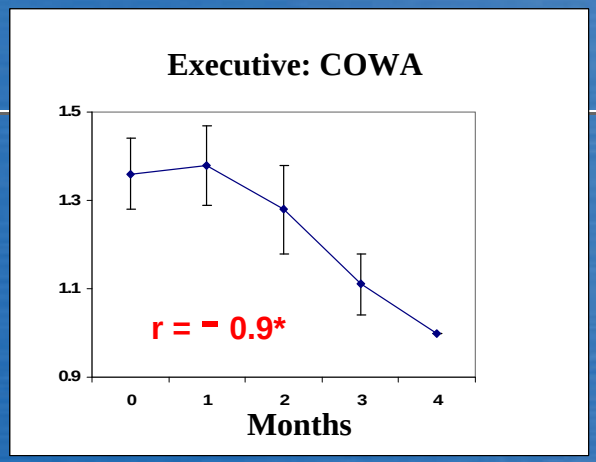


Meyers JCO 2004

Mean NCF Scores in Short vs Long-term Survivors

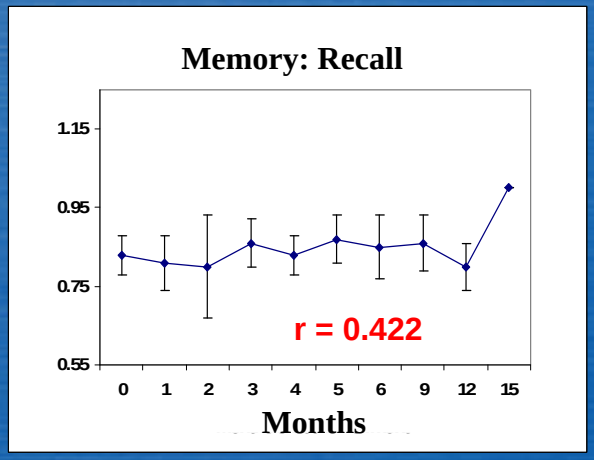
Mean scores

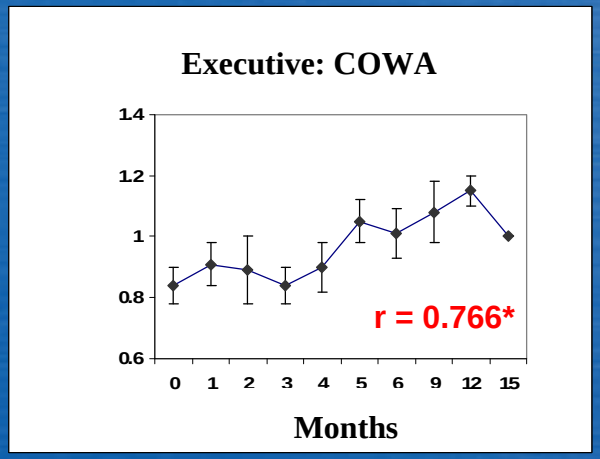




← 4 months survivors

Mean scores





← 15 months survivors

*r - Spearman's correlation between mean scores and time, * statistical significance*

Very High Brain Relapse After Surgery if WBRT is Omitted

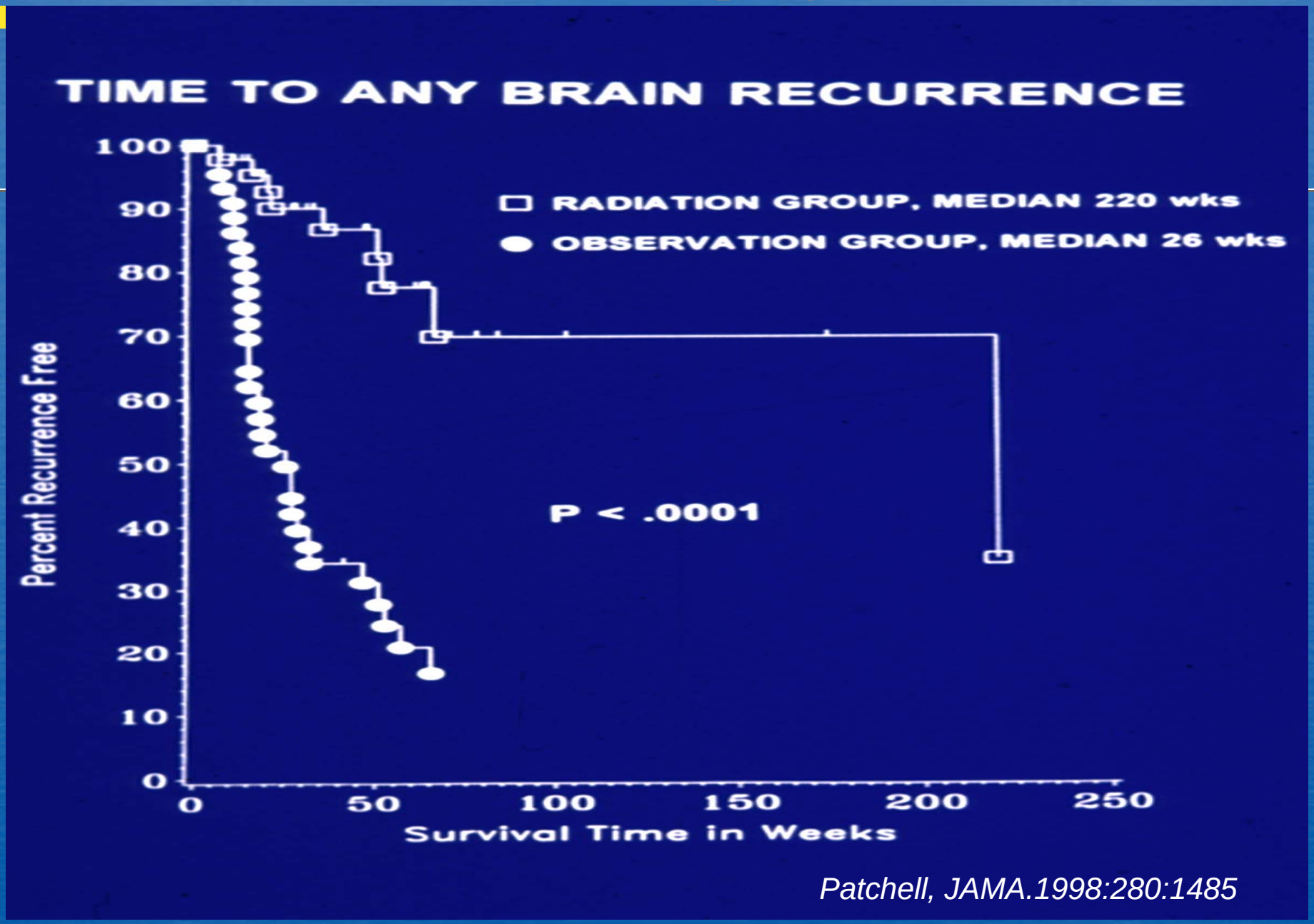
Recurrence	No RT (46)	WBRT (49)	RR	p
Any brain	70%	18%	~3	<.001
Original	**46%**	**10%**	**3.6**	**<.001**

Complete resection without WBRT leads to 70% actuarial relapse

This is a relative risk of 3

Patchell, JAMA.1998:280:1485

Tumor Growth Occurs Rapidly Without WBRT



Patchell, JAMA.1998:280:1485

Neurocognitive Decline by HVLT

	Mean Probability of NCF Decline
SRS N = 28	23%
SRS+WBRT N = 30	49%

96% conf

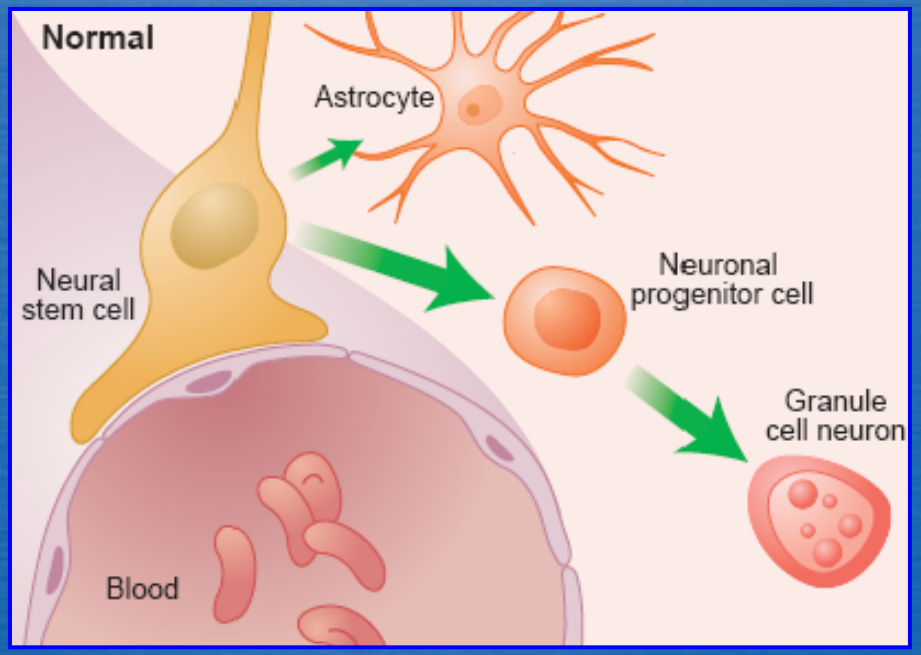
Eric Chang, MDACCC

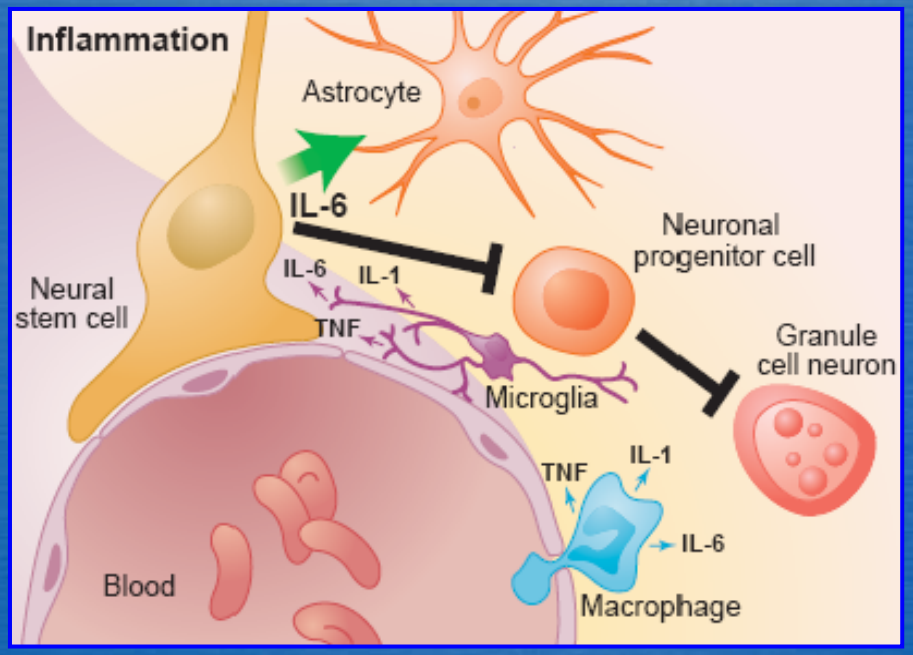
Where is the Balance?

- NCF deterioration occurs early and often.
- We have analyzed the time course of NCF decline employing 8 prospectively measured domains in 208 brain metastases patients treated with 30 Gy WBRT and have found that:
  - **Median time to NCF deterioration was longer in good than in poor responders**.
  - **Memory was most susceptible to early decline**, even in patients with non-progressing brain metastases: *the role of the hippocampus*

Li J, Bentzen SM, Renschler M, et. al. J. Clin. Oncol.

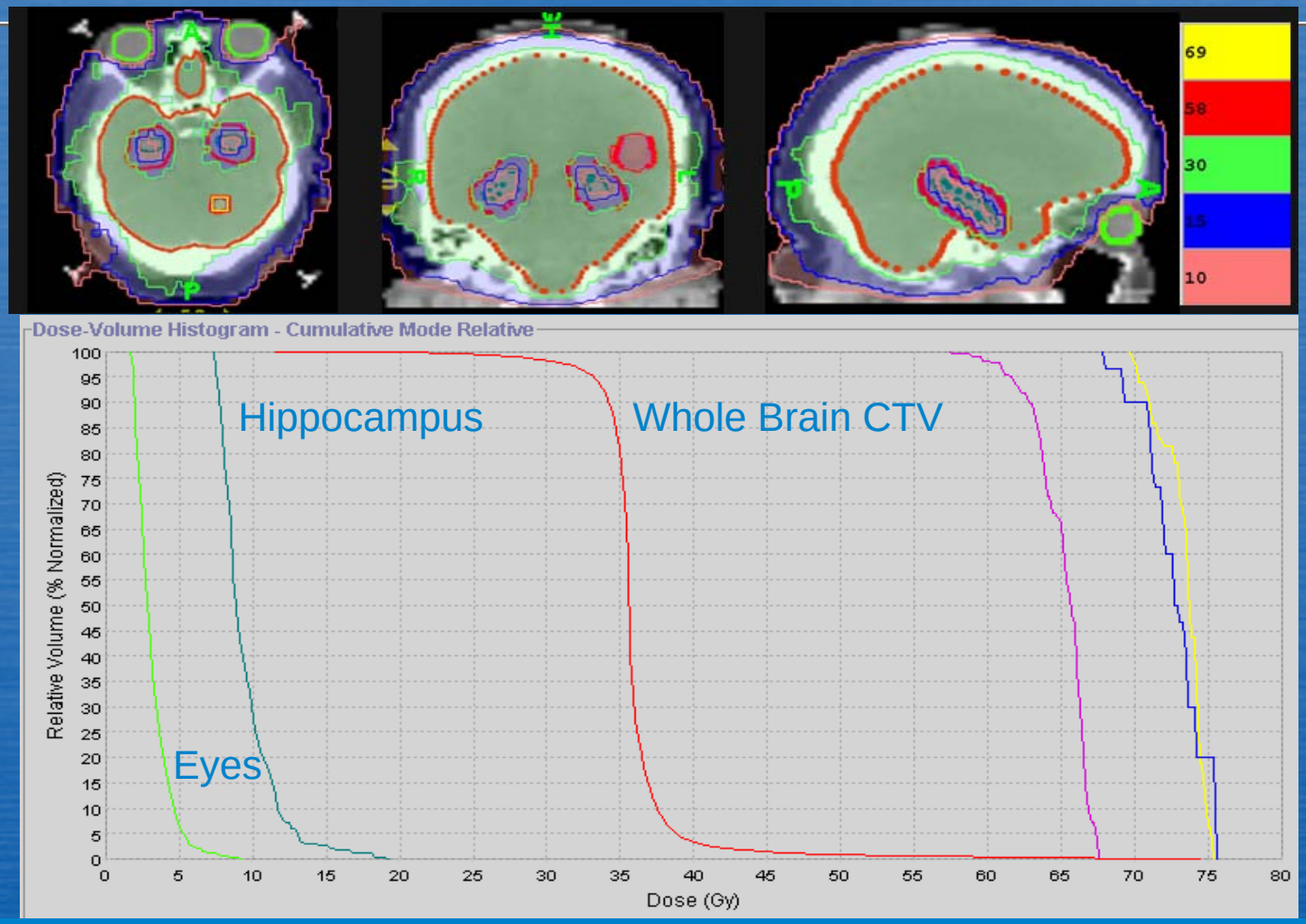
Neural stem cells in the hippocampus





📖 Kempermann & Neumann *Science* 302: 1689 (2003)

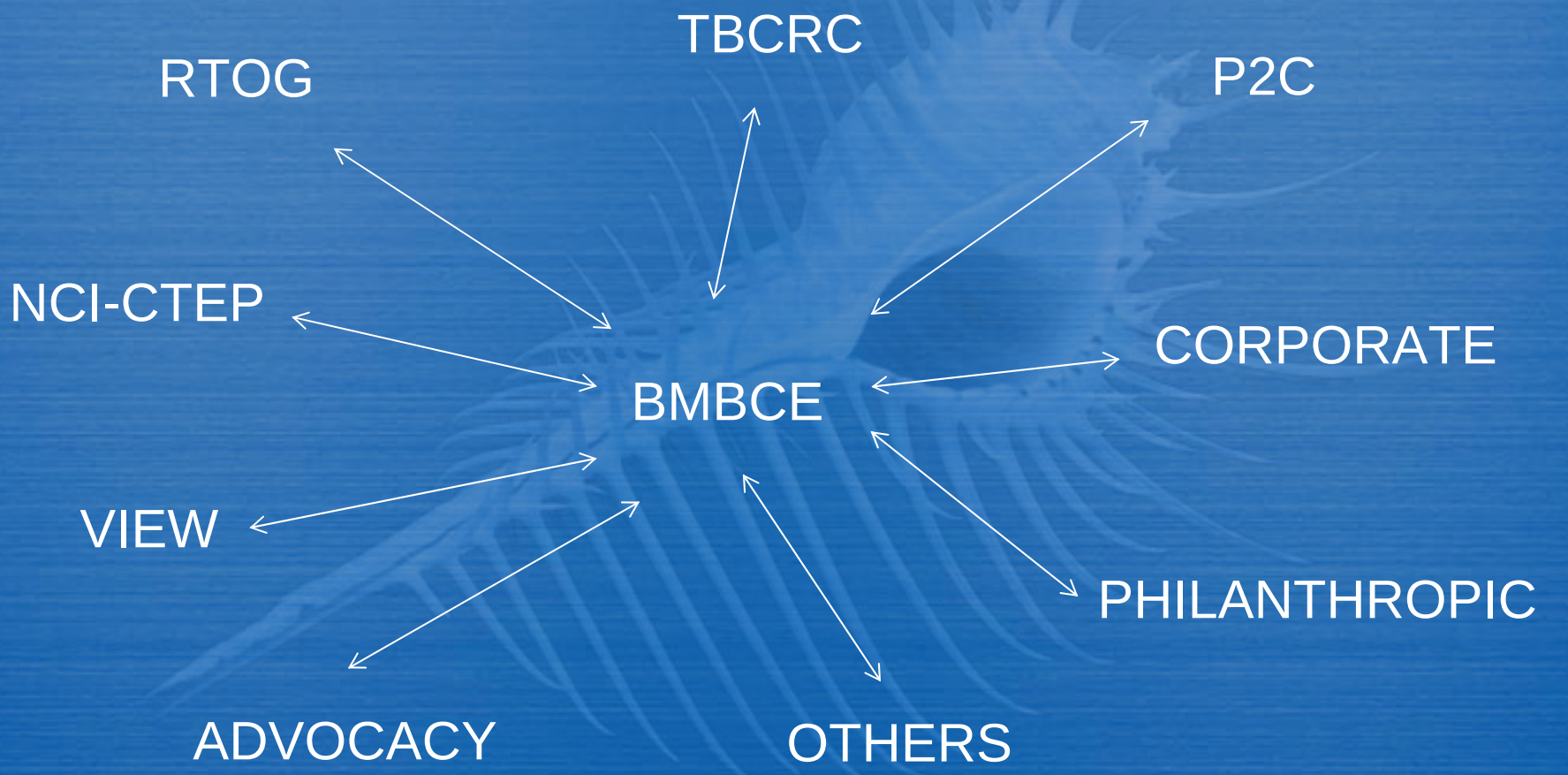
HA-WBRT in conjunction with selective boosting of brain metastases



Other Strategies

- NMD receptor agonists, e.g. Memantine are beneficial in Alzheimer's
  - RTOG is testing this in a phase III trial, 0614
- Renin-Angiotensin (ACE) inhibitors, e.g. Ramipril
- Intranasal inhaled insulin

Brain Metastases in Breast Cancer Effort



Major Goals

- Understand the biology (biobank)
- Identify “at-risk” patients
- Prevention
- Screening
- Improve therapeutic choices
- Identify predictors of outcome

Trial Categories

- Prophylaxis in high-risk patients
- Surgical trials
  - Drug targeting questions
  - Role in >1 met
- Post-op trials
  - RT +/- test agent
  - Hippocampal sparing WBRT
  - Test agent +/- RT

Trial Categories

- Radiosurgery-treated patient
  - Role of WBRT (NCCTG trial)
  - Novel therapeutics to prevent brain relapse
- WBRT patients
  - RT +/- test agent (eg PARPI or HDACs)
  - Hippocampal sparing WBRT

Trial Categories

- Untreated Stable Patients
  - Novel therapeutics to prevent brain progression
- Post-RT progression
  - Test Agent