Neurologic Complications of Cancer Treatment

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DISCLOSURES

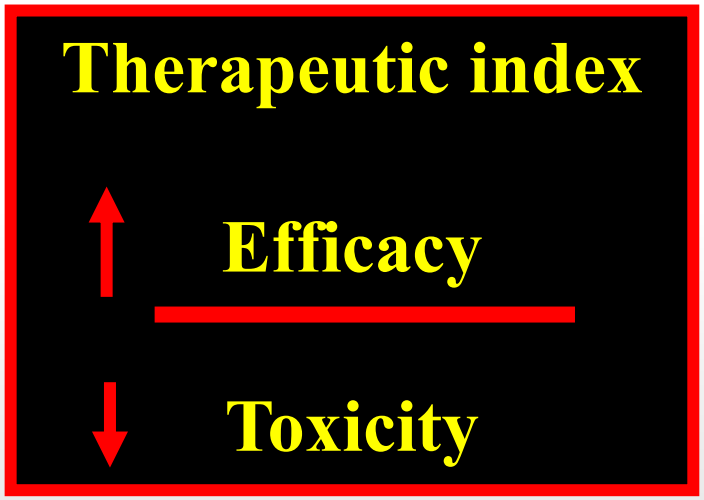
No conflict of interest with respect to this presentation

Discuss off-label use of memantine and duloxetine

Learning objectives

- Understand relevance of neurologic complications of cancer treatment
- Describe long term side effects of RT in the brain and potential preventive/therapeutic strategies
- Define peripheral nervous system chemotherapy induced toxicity and efficacy of treatment

The argument: risk against benefit



I WILL FOLLOW that system of regimen which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous.

Therapeutic ratio of cancer treatment

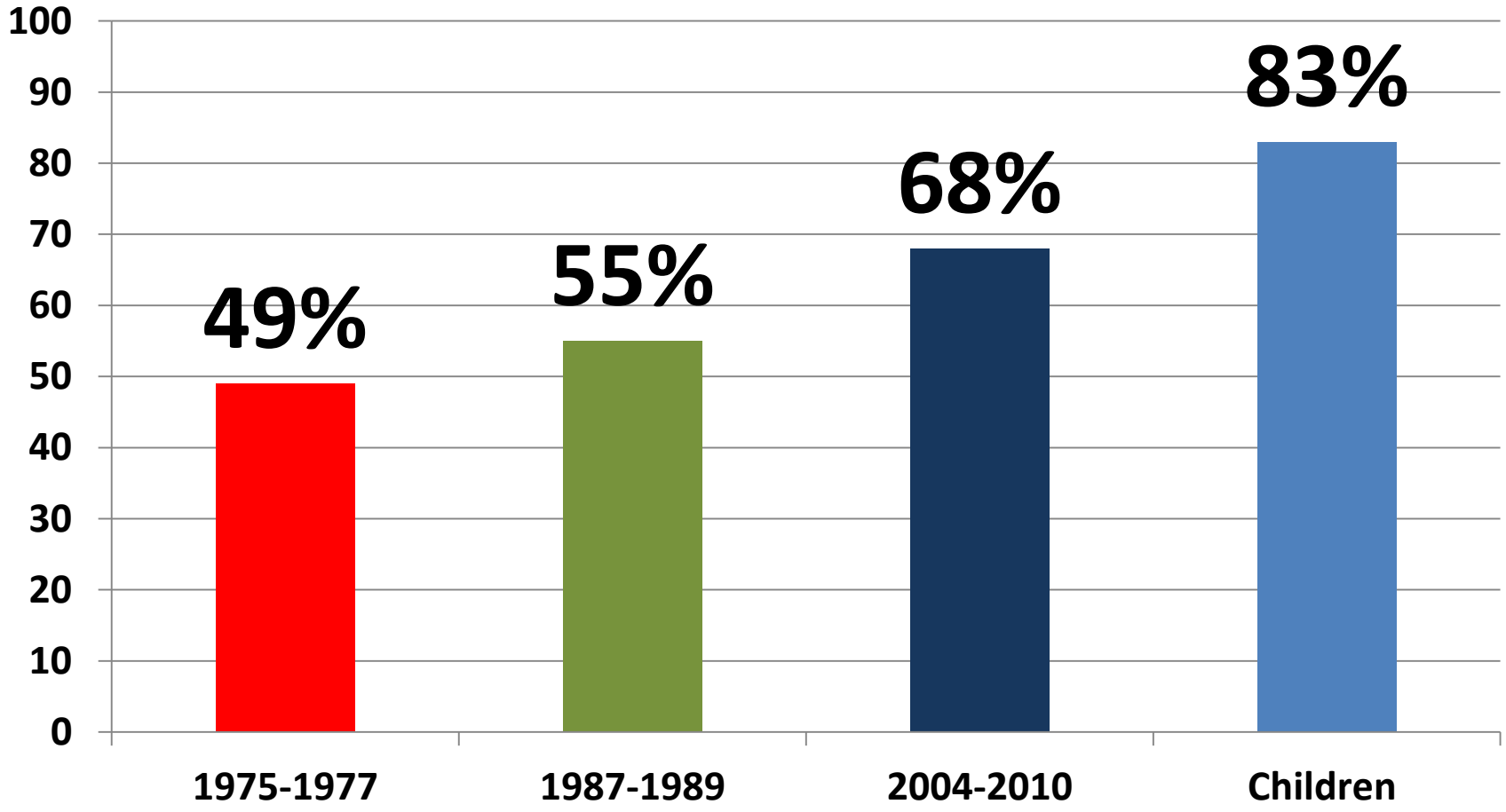
MODES OF TREATMENT

MODE	GOAL	SURVIVAL	TOXICITY
CURATIVE	SURVIVAL	PROLONG	MAY BE ↑
PALLIATIVE	Q O LIFE	?	LOW
TERMINAL	Q O LIFE	NO	NONE

(ASHBY ET AL, BMJ 1991)

Patients with cancer are surviving longer

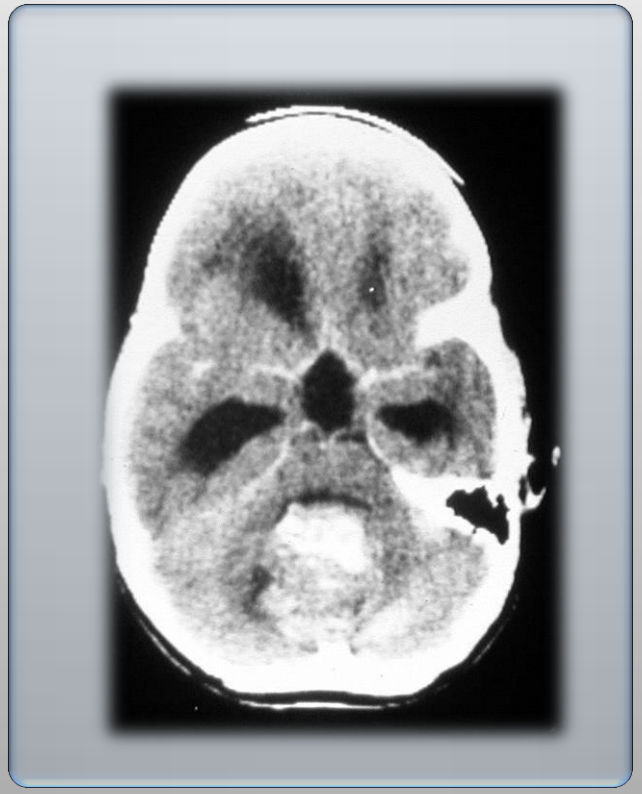
Trends in 5-year survival rates for all cancers



Source: American Cancer Society: Cancer Statistics 2015 and ASCO 2015

Setting the stage

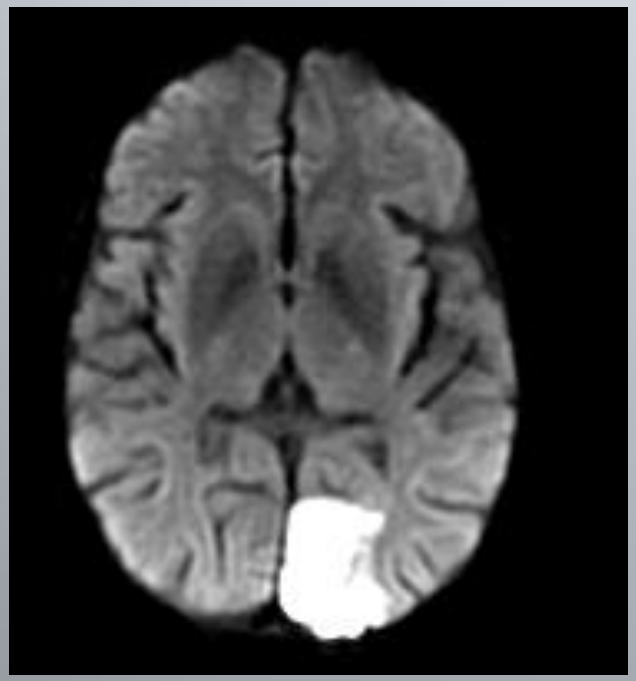
In 1986 a 13 year old girl presents with symptoms of increased intracranial pressure and ataxia

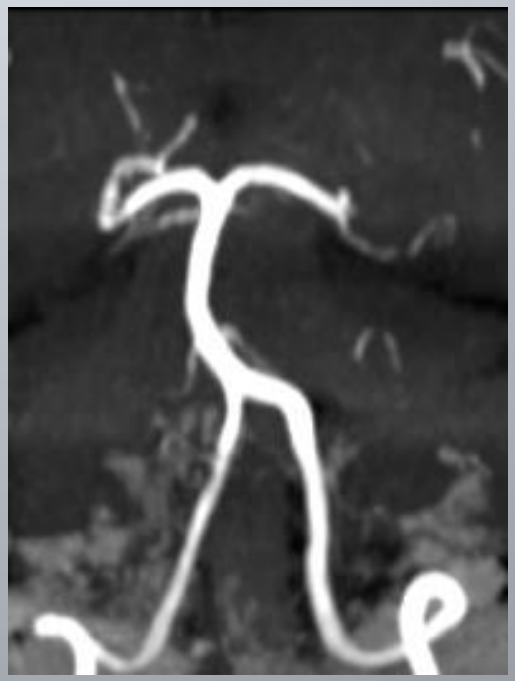


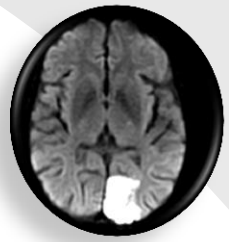
Tumor is resected and pathology reveals medulloblastoma. Treated with craniospinal RT and chemotherapy

Setting the stage

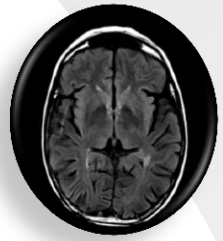
In 2014 (28 years after tumor diagnosis) at age 41 she presents with a 10 day history of right visual loss and left side headaches



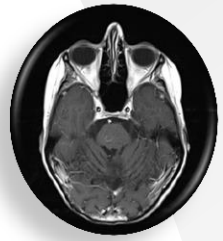




Stroke



Stroke-like Migraine Attacks after RT



Cavernomas-hemorrhage

DELAYED CEREBRAL VASCULOPATHY ASSOCIATED WITH RADIATION FOR PEDIATRIC TUMORS

Moyamoya syndrome*

* http://radiopaedia.org/images/537643

Cytotoxic chemotherapy is a "double edged sword"

Toxicity requiring to stop chemotherapy:

1. Bone marrow suppression

2. Renal complications

3. Nervous system complications

NEUROLOGIC COMPLICATIONS EMERGING AS A MAJOR CAUSE OF CHEMOTHERAPY DOSE LIMITING TOXICITY AS OTHER TOXICITIES ARE BETTER MANAGED AND NEW AGENTS ARE APPROVED

CYTARABINE

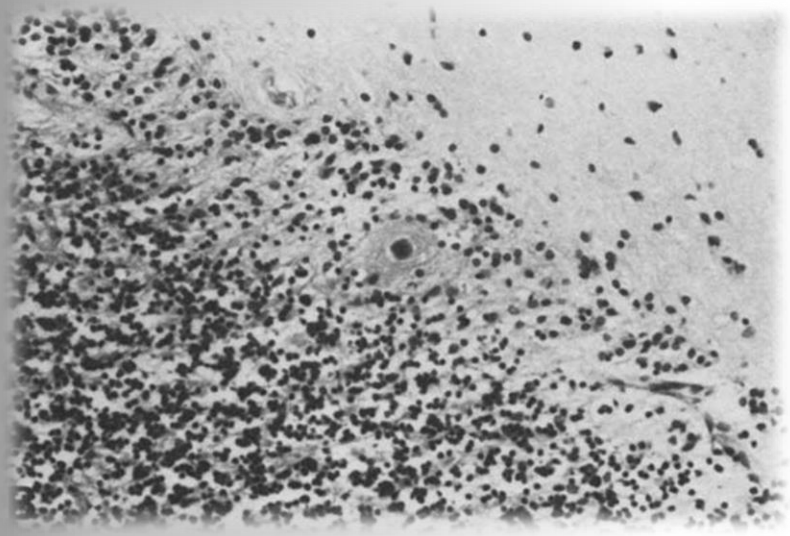
HD CYTARABINE IN THE PAST LIMITED BY MYELOSUPPRESSION

AS GROWTH FACTORS AVAILABLE DOSE LIMITED BY CEREBELLAR TOXICITY

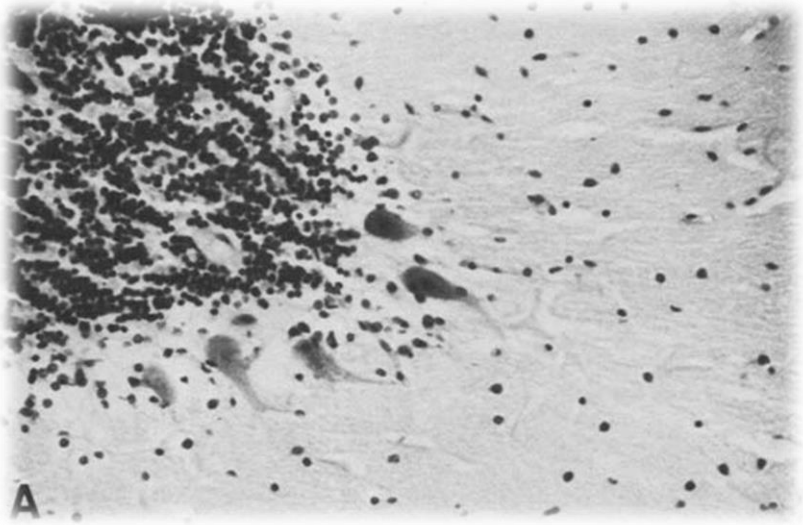
AGE AND DOSE (> 48 gm/m2) ARE PREDICTORS OF TOXICITY

CYTARABINE

A 47 year old man with diagnosis of Hodgkin's lymphoma developed a cerebellar syndrome after cumulative dose of 30 gm/m2 of cytarabine- He required of additional doses up to 60 gm/m2



Patient cerebellum



Normal cerebellum

J Clin Oncol 3:613-616. © 1985

BEVACIZUMAB
Reversible Posterior Leukoencephalopathy Syndrome

A REVERSIBLE POSTERIOR LEUKOENCEPHALOPATHY SYNDROME

JUDY HINCHEY, M.D., CLAUDIA CHAVES, M.D., BARBARA APPIGNANI, M.D., JOAN BREEN, M.D., LINDA PAO, M.D., ANNABEL WANG, M.D., MICHAEL S. PESSIN, M.D., CATHERINE LAMY, M.D., JEAN-LOUIS MAS, M.D., AND LOUIS R. CAPLAN, M.D.

N Engl J Med 1996;334:494-500.

Reversible Posterior Leukoencephalopathy Syndrome and Bevacizumab

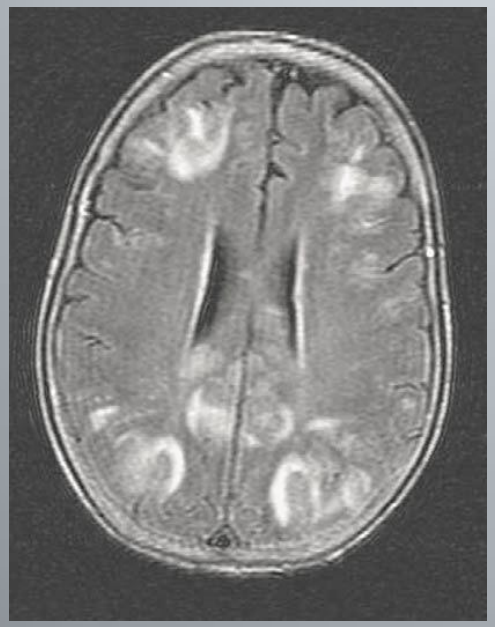
N Engl J Med 354;9, 2006.

Posterior Reversible Encephalopathy Syndrome in Patients With Cancer

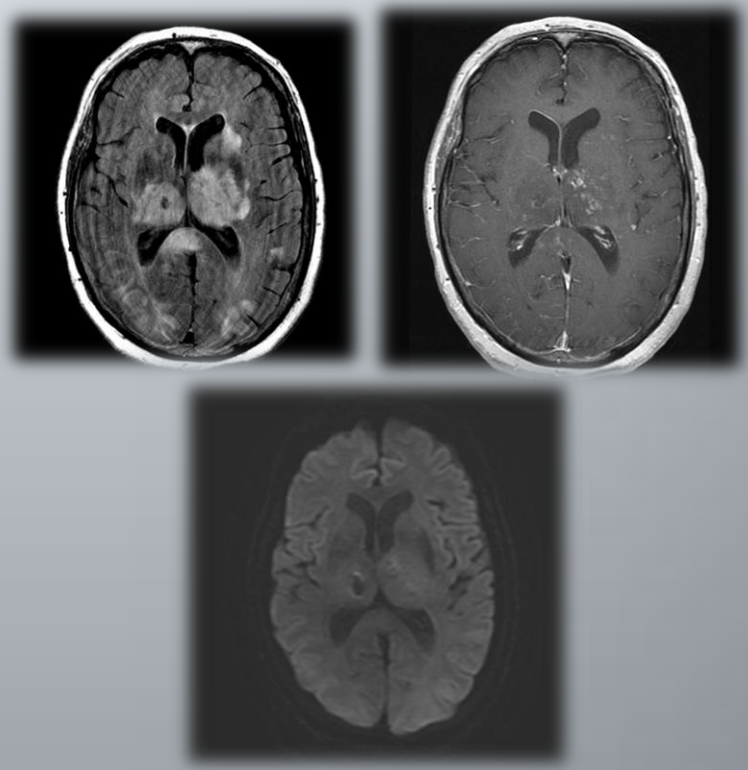
BEVACIZUMAB

Reversible Posterior Leukoencephalopathy Syndrome

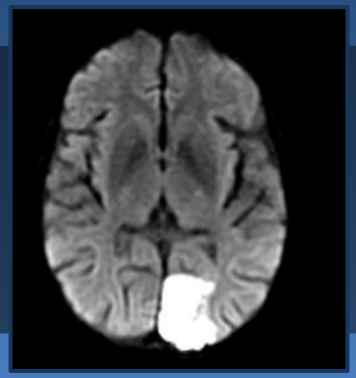
Illustrative cases



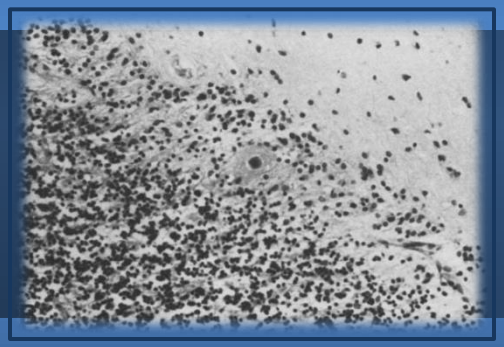
NEJM 354;9 March 2, 2006



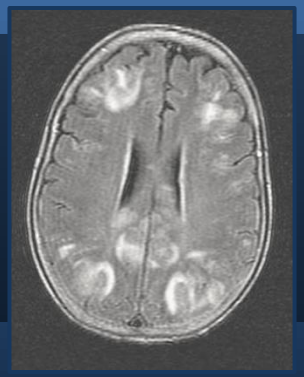
SUMMARY KEY MESSAGES



Patients with cancer are living longer and therefore more prone to have delayed neurologic complications



Chemotherapy induced neurologic complications can be dose limiting toxicity



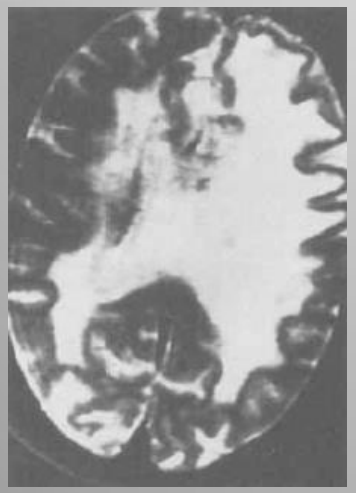
New drugs in clinical trials with potentially unrecognized as yet neurologic complications

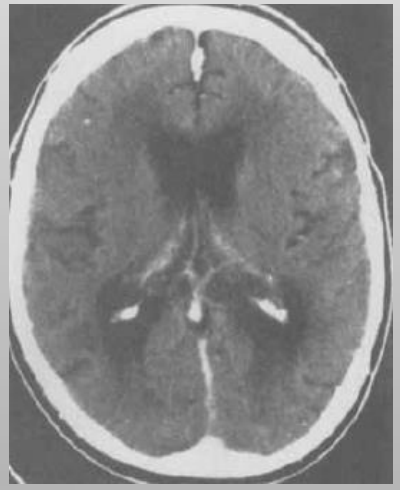
DELAYED RADIATION NEUROTOXICITY

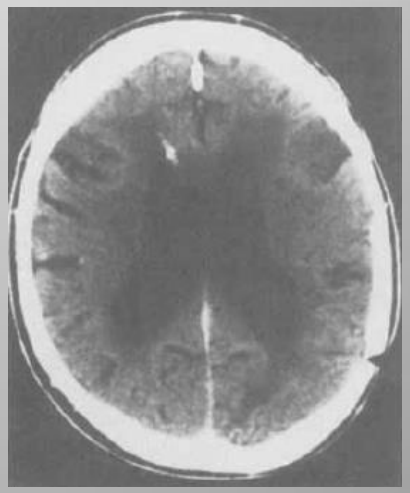
Radiation-induced dementia in patients cured of brain metastases

Lisa M. DeAngelis, MD; Jean-Yves Delattre, MD; and Jerome B. Posner, MD

NEUROLOGY 1989;39:789-796

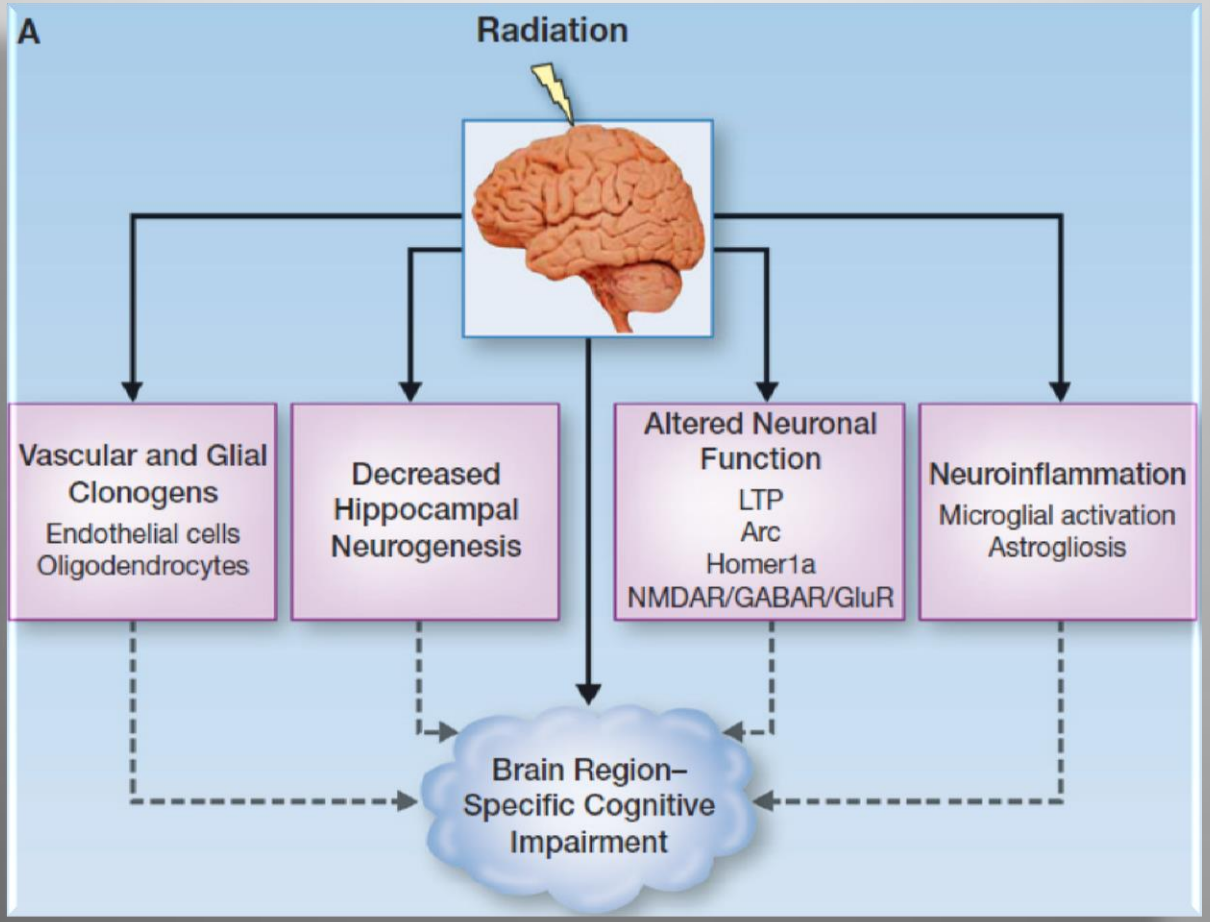






Patients surviving more than a year after WBRT frequently develop progressive cognitive impairment characterized by leukoencephalopathy, ventricular dilation and cortical atrophy in brain imaging studies.

Potential mechanisms of radiation induced cognitive impairment



Clin Cancer Res; 19(9); 2294–300.

RADIATION NEUROTOXICITY

The very young and the old are at higher risk.

The fractionation and total dose that will decrease the risk is uncertain

Identify patients who can be long term survivors and at risk to avoid WBRT

A phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. (ASCO 2015)

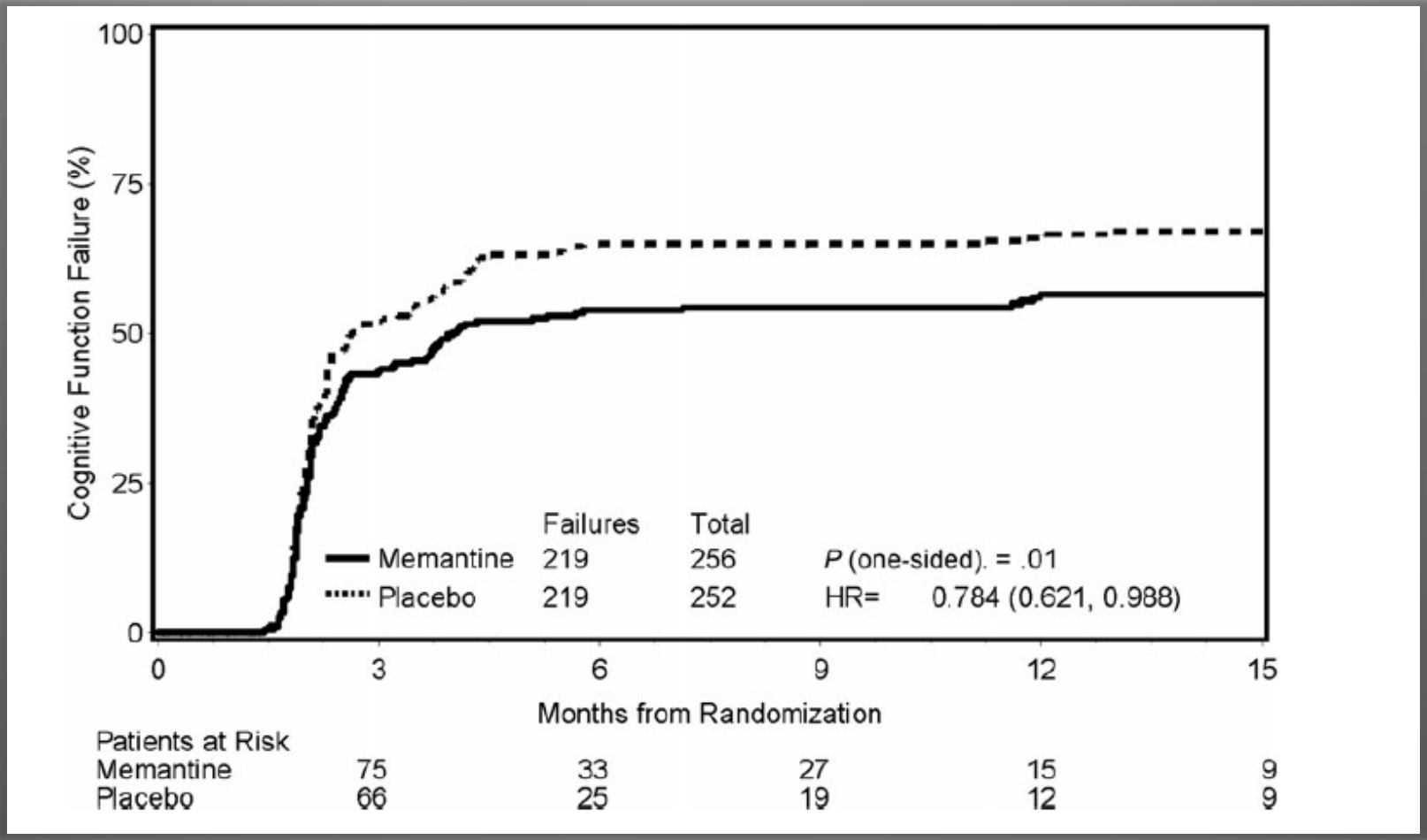
	SRS	SRS + WBRT	p value
Number	111	112	
Cognitive deterioration at 3 m	91.7%	63.5%	0.0007
Delayed recall at 3 m	19.7%	51.1%	0.0009
Median survival	10.4 m	7.4m	NS
CNS failure at 3 m	24.7%	6.3%	p<0.0001
CNS failure at 6 m	35.4%	11.6%	p<0.0001

Memantine for the prevention of cognitive dysfunction in patients receiving WBRT: a randomized, double-blind, placebo-controlled trial

	554 Patients with brain metastases received 37.5 Gy WBRT	
	memantine	Placebo
Baseline	235	238
8-weeks	129	139
16-weeks	86	93
24-weeks	71	78
52-weeks	39 (17%)	40 (17%)

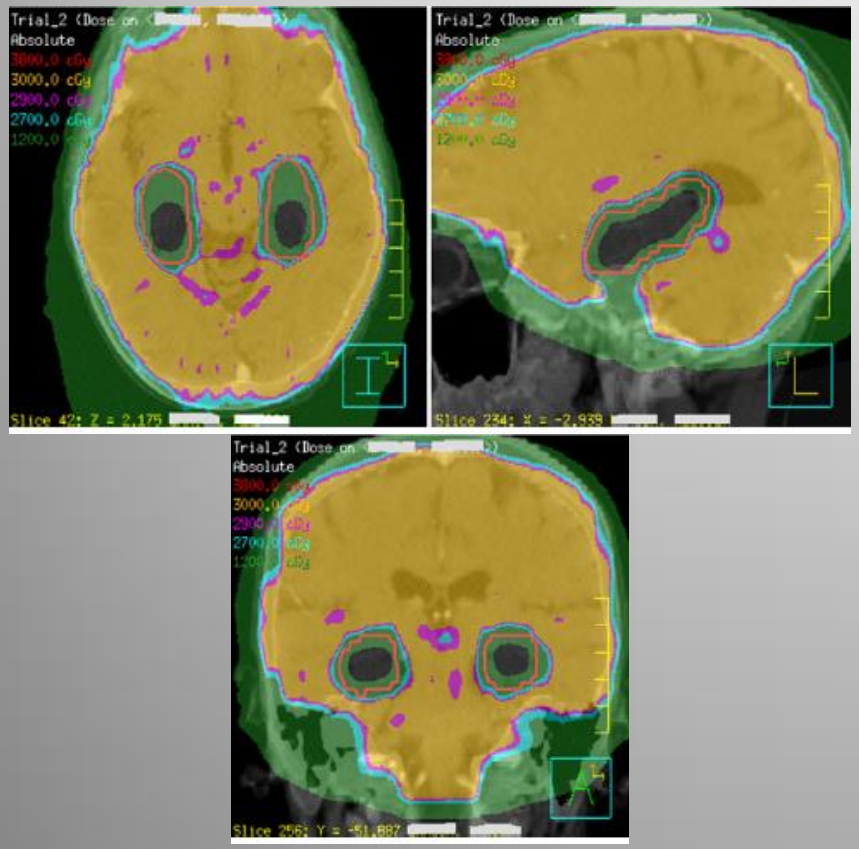
Neuro-Oncology 15(10):1429–1437, 2013.

Potential mechanisms of radiation induced cognitive impairment

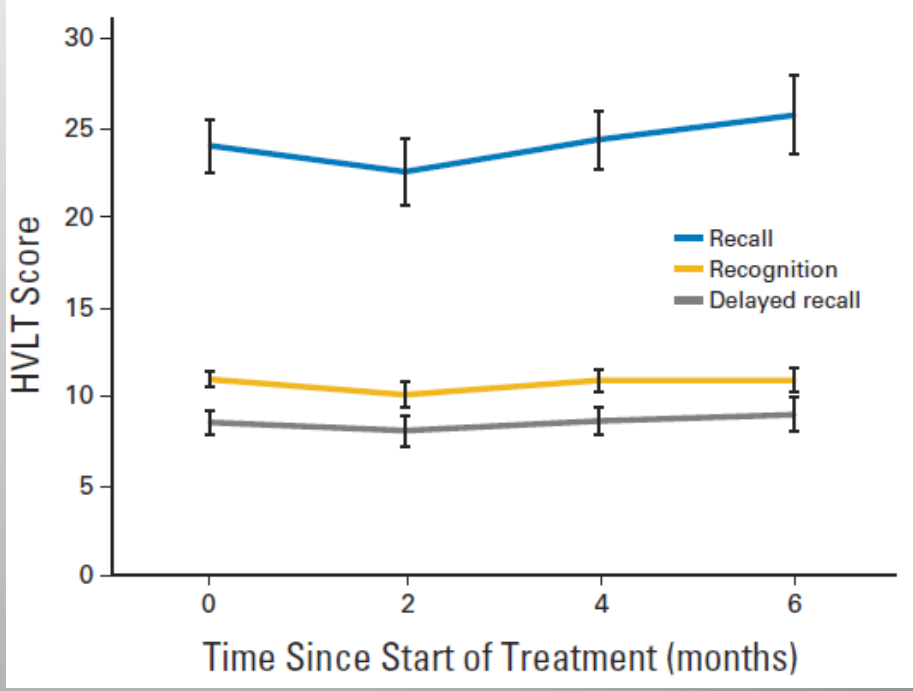


Neuro-Oncology 15(10):1429–1437, 2013.

Prevention and treatment of radiation neurotoxicity
Hippocampal avoidance

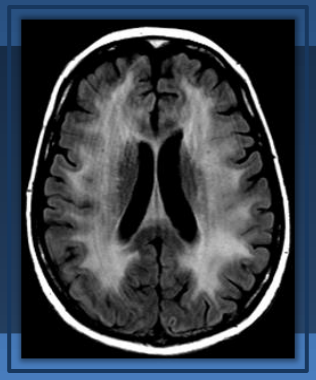


Radiotherapy and Oncology 97 (2010) 370–376

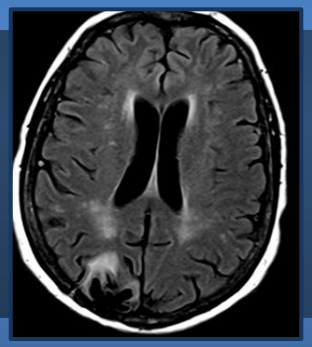


J Clin Oncol 32:3810-3816. © 2014

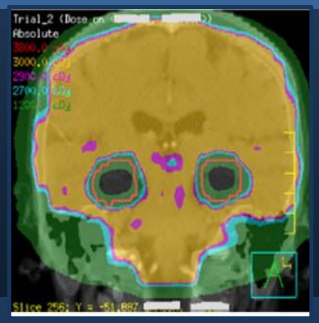
SUMMARY KEY MESSAGES



As patients with brain metastases live longer the neurotoxicity of WBRT gains is more prevalent



Stereotactic radiosurgery is a reasonable option for patients with 1-3 brain metastases



Options to decrease radiation toxicity are being studied, highlight the need for more targeted therapies

Chemotherapy induced neuropathy

	BONE MARROW	RENAL	NEUROPATHY
Diagnosis	Objective	Objective	Subjective
Life-threatening	Yes	Yes	No
Onset	Acute	Acute	Delayed
Timing	On therapy	On therapy	After therapy
Recovery	Rapid	Rapid	Slow

Myth: Chemotherapy induced neuropathy is not a problem

CHEMOTHERAPY INDUCED NEUROPATHY IS FREQUENT BUT UNDERREPORTED AND UNDERDIAGNOSED

CHEMOTHERAPY INDUCED NEUROPATHY IMPACTS QUALITY OF LIFE IN THE ACUTE SETTING AND FOR LONG TERM SURVIVORS

PREVENTING, AVOIDING, AND TREATING THIS COMPLICATION IS THE ROLE OF THE NEUROLOGIST

Chemotherapy agents that are recognized nerve offenders

Family	Drugs	Neuropathy	Mechanism?
Platin compounds	Cisplatin Oxaliplatin	30-60% 74%	**Binds DNA-DRG-Apoptosis**
Taxane derivatives	Paclitaxel Docetaxel	60-70% less	Disordered microtubules
Vinca alkaloids	Vincristine Vinblastine	100% less	Disrupt microtubule
Proteasome inhibitor	Bortezomib Carfilzomib	30-60% less	Uncertain
Immunemodulators	Thalidomide Lenalidomide	100% less	Disrupt microtubule

Preventive intervention for CIN Pharmacologic

Drug	Action	Evidence	Drugs
ACTH analogue	Neurotropic	Conflicting	CDDP
Amifostine	Detoxicant	Negative	CDDP/Paclit
Glutathione	Detoxicant	?	CDDP/OXAL
hLIF	Unknown	Negative	Paclit+Carbo
Glutamine	NGF	?	Paclit
Vitamin E	Scavenger	Negative	Paclit/CDDP
Carbamazepine	Voltage Na	?	OXAL
Calcium/Mg	Voltage Na	Negative	OXAL

There is no evidence that any of these drugs prevent the development of chemotherapy induced neuropathy (ASCO 2014)

Treatment for CIN

Drug	Action	Evidence	Drugs
Lipoic acid	Neurotropic	?	CDDP
Glutamine	NGF	Suggestive	Paclitaxel
Calcium/Mg	Voltage Na	Negative	OXAL
Vitamin E	Scavenger	Suggestive	Paclit/CDDP

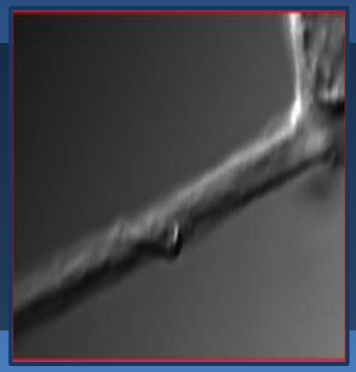
There is no evidence that these drugs are effective in repairing the nerve damage of chemotherapy induced neuropathy

Pain treatment for CIN

Drug	Evidence	Drugs
Duloxetine	Yes	Oxal/CDDP
Gabapentin	?	All
TCA	?	All
Topical Baclofen/amitriptyline/Ketamine	?	All

Duloxetine can be offered to patients with chemotherapy induced neuropathy. Others can be offered but no evidence

SUMMARY KEY MESSAGES



CI-NEUROPATHY IS FREQUENT BUT UNDERREPORTED AND UNDERDIAGNOSED

THERE ARE NO PROVEN PROPHYLACTIC /THERAPEUTIC OPTIONS. DULOXETINE HELPS PAIN

PREVENTING AVOIDING AND TREATING THIS COMPLICATION IS THE ROLE OF THE NEUROLOGIST

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