Addressing Neurocognitive Late Effects in Brain Tumour Survivors

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UHN

No Disclosures

Objectives

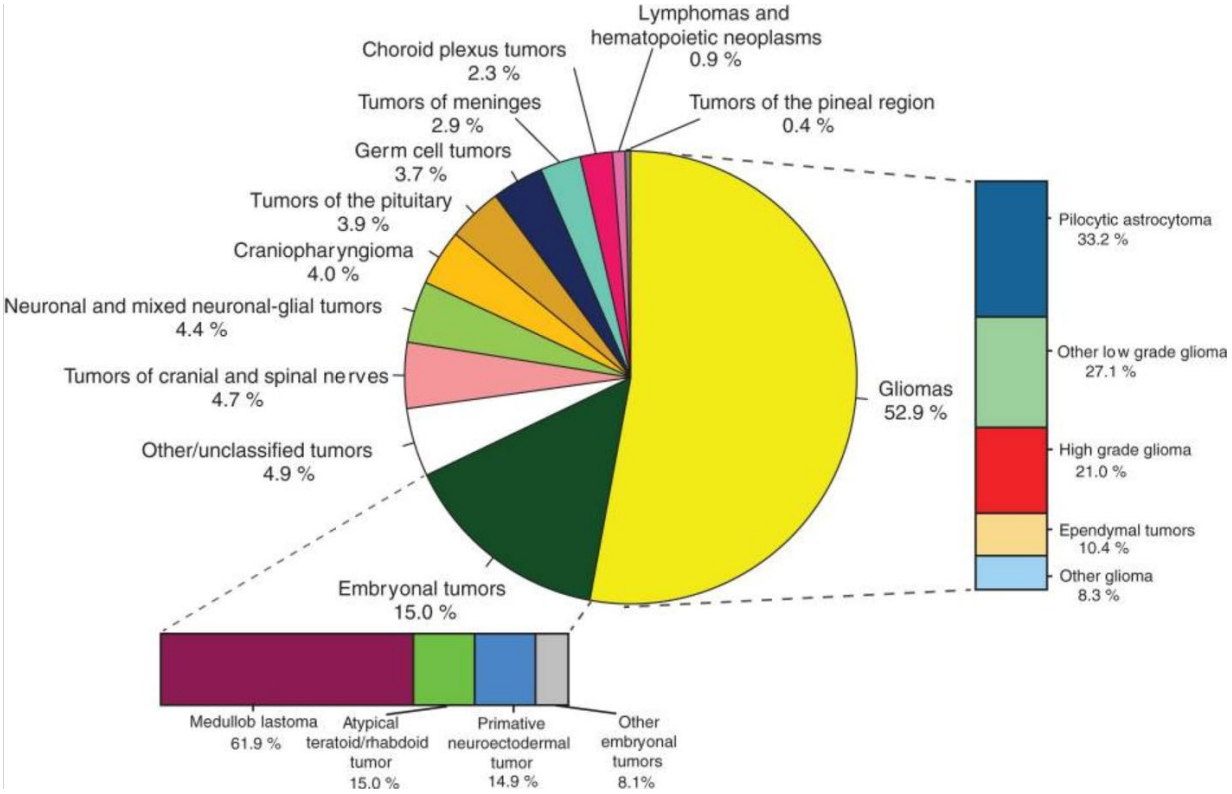
1. Understand risk factors for neurocognitive late effects in children with CNS tumors

2. Review changes in treatment paradigms to reduce neurocognitive late effects

3. Discuss strategies to improve neurocognition following treatment for CNS tumors

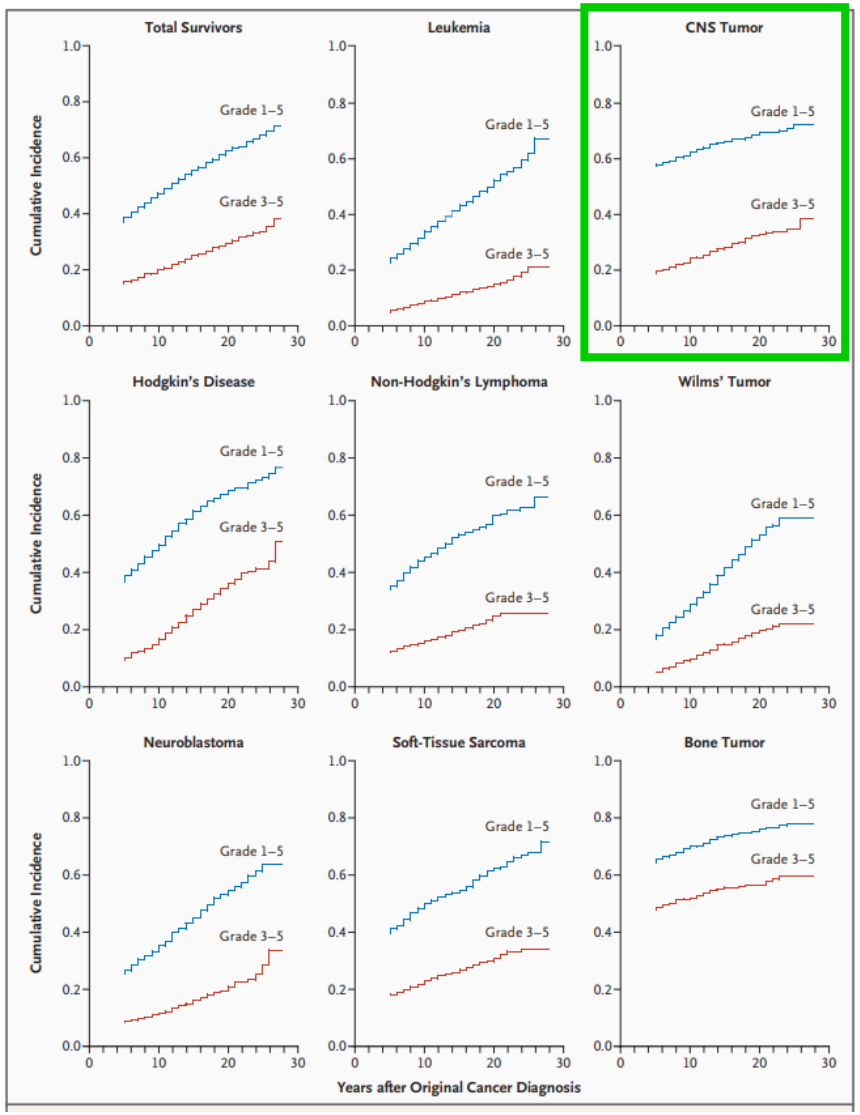
Background

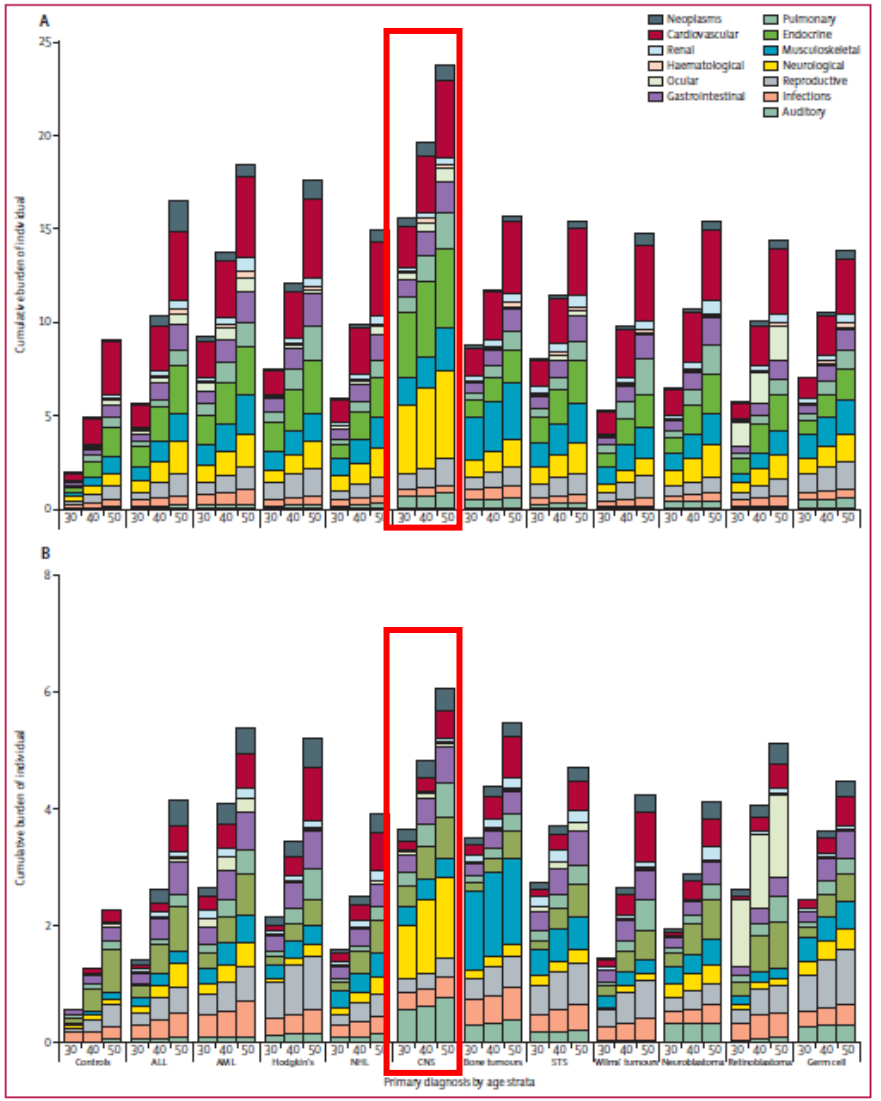
- Central nervous system (CNS) tumors are the 2nd most common cancer in children
- Most common cause of cancer-related death in pediatrics.
- 10-year survival rates ~70%



Ostrom *et al.* Neuro Oncol 2015

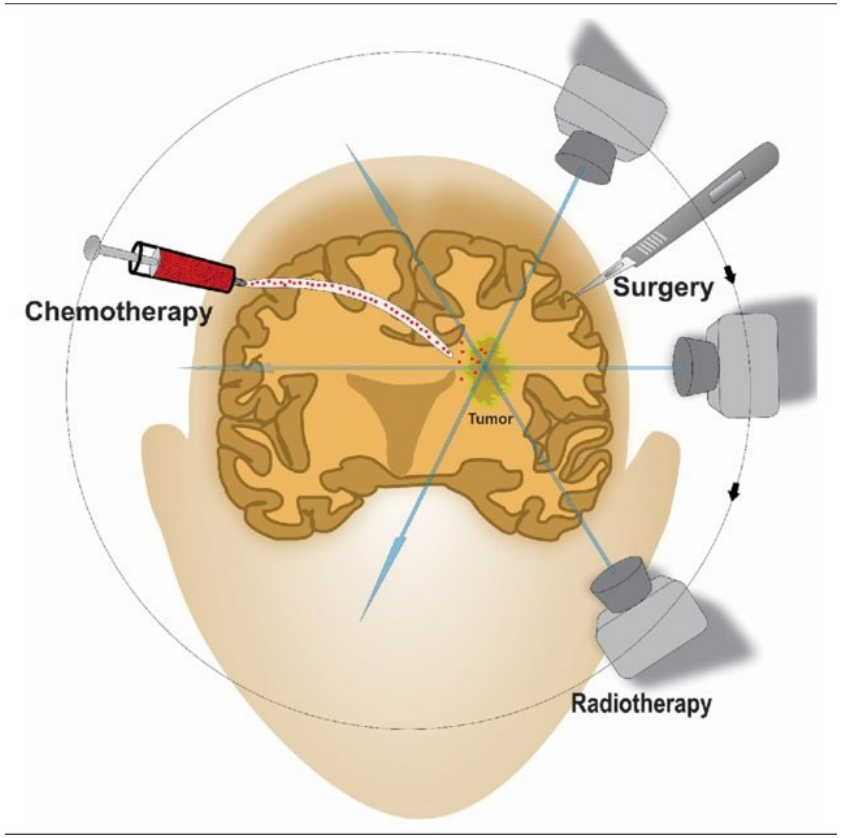
There is significant morbidity for survivors of CNS tumors

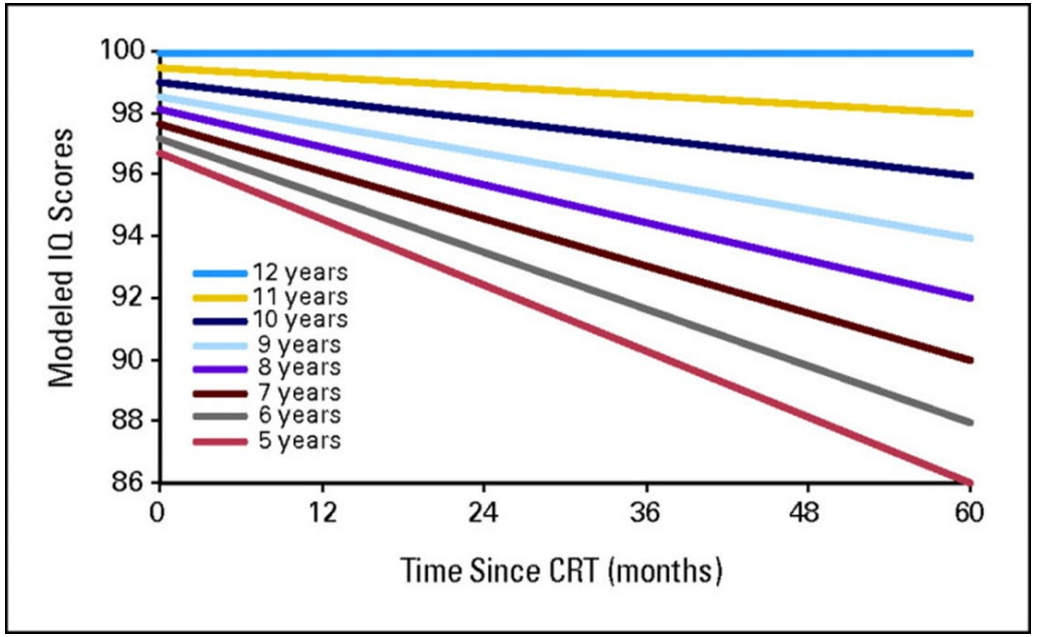




Oeffinger *et al.* N Engl J Med 2006
Bhakta *et al.* Lancet 2017

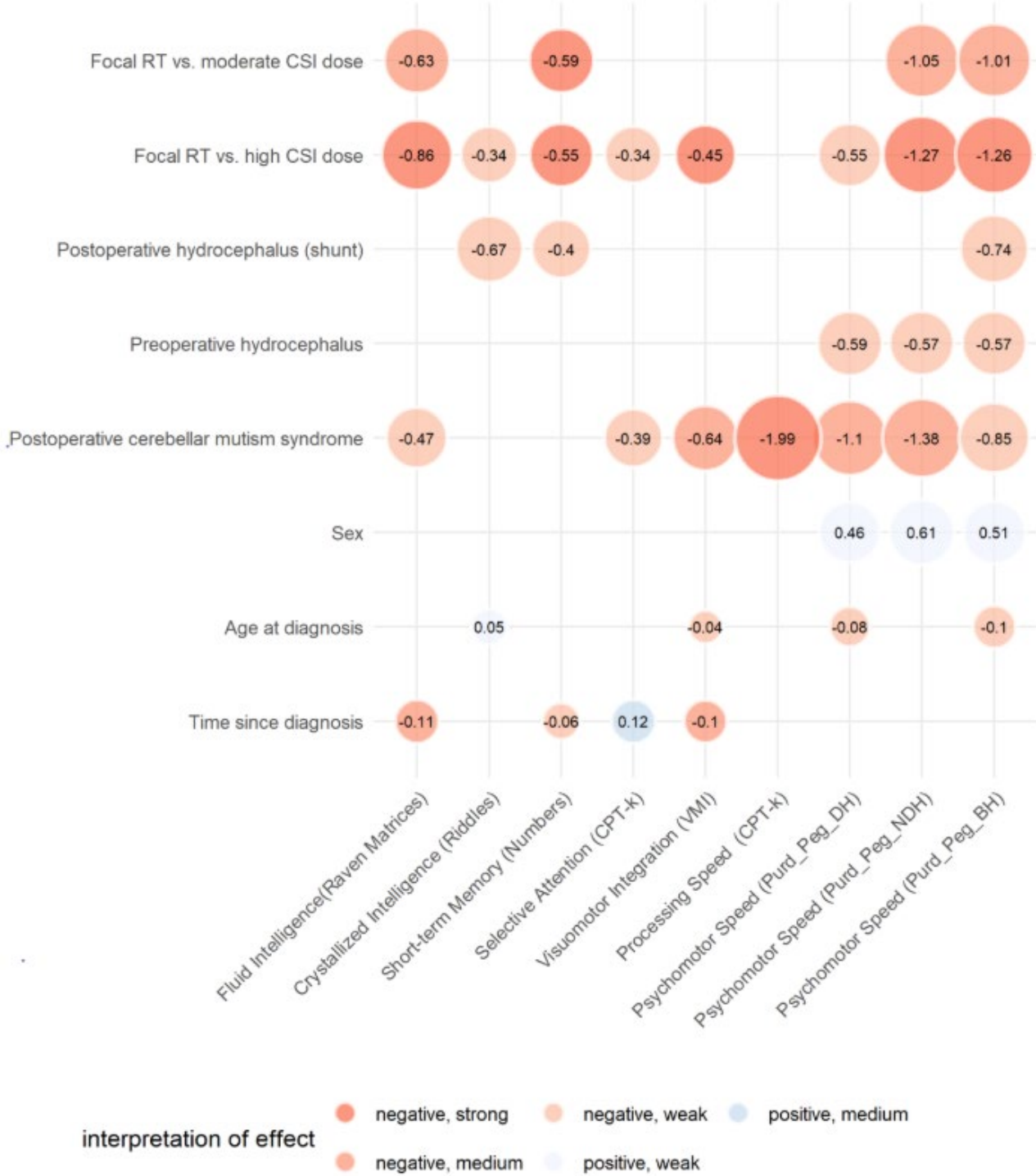
Multimodal treatment required with risk for neurocognitive deficits





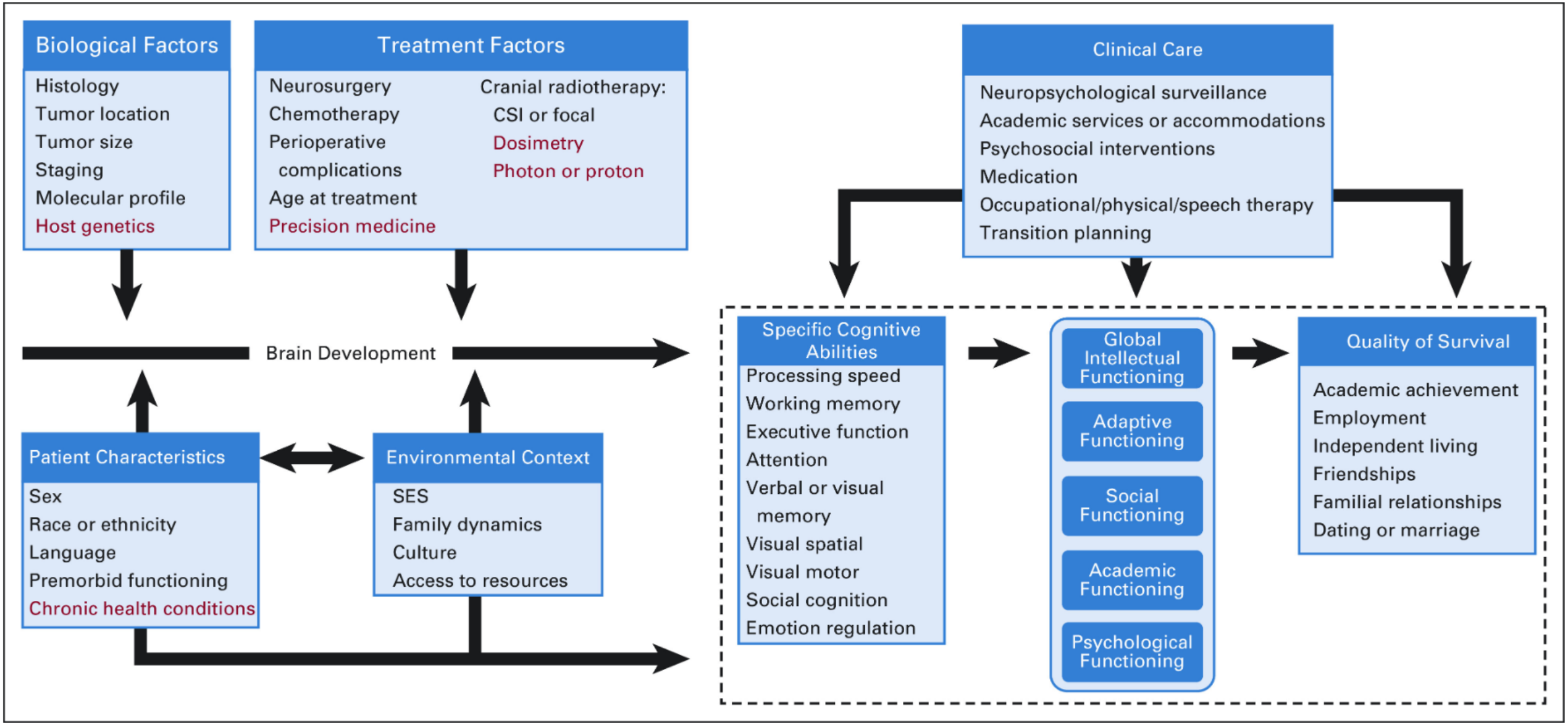
Modelled intelligence quotient (IQ) scores after CNS therapy by age (www.cancer.gov)

Mehrabian *et al*, Technol Cancer Res Treat, 2022



Mynarek *et al*. Neuro Oncol 2024

Complex risk factors for neurocognitive deficits

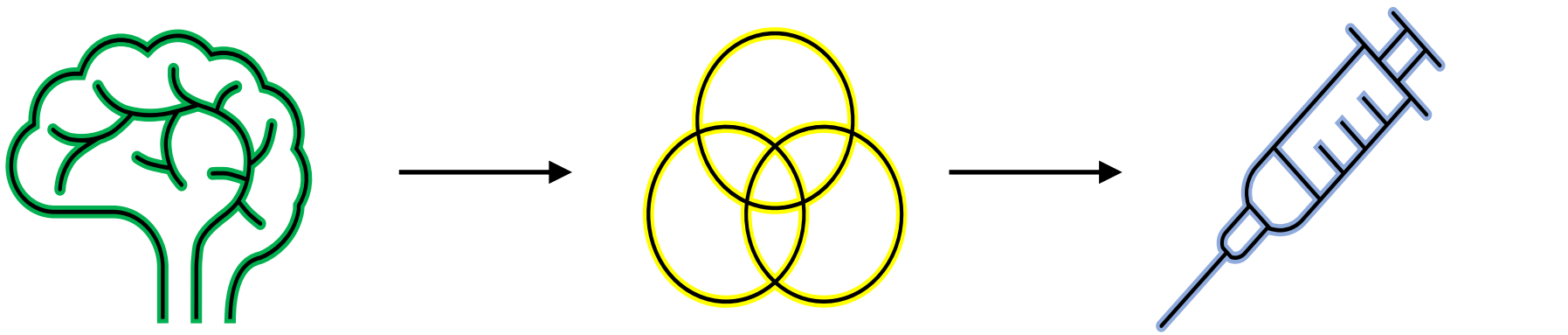


Oyefiade *et al*. J Clin Oncol 2021

Treatment Risk Factors

Starting with…. Medulloblastoma

Treatment Paradigm:



Surgery

Radiation
(Brain and
Spine)

Chemotherapy

Molecular Subgroups of Medulloblastoma

CONSENSUS	WNT	SHH	Group 3	Group 4
Cho (2010)	C6	C3	C1/C5	C2/C4
Northcott (2010)	WNT	SHH	Group C	Group D
Kool (2008)	A	B	E	C/D
Thompson (2006)	B	C', D	E, A	A, C

DEMOGRAPHICS

Age Group: infant, child, adult

Gender: ♀ ♂

	WNT	SHH	Group 3	Group 4
Age Group				
Gender	♂♂:♀♀	♂♂:♀♀	♂♂:♀	♂♂:♀

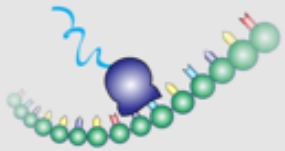
CLINICAL FEATURES

	WNT	SHH	Group 3	Group 4
Histology	classic, rarely LCA	desmoplastic/nodular, classic, LCA	classic, LCA	classic, LCA
Metastasis	rarely M+	uncommonly M+	very frequently M+	frequently M+
Prognosis	very good	infants good, others intermediate	poor	intermediate

GENETICS

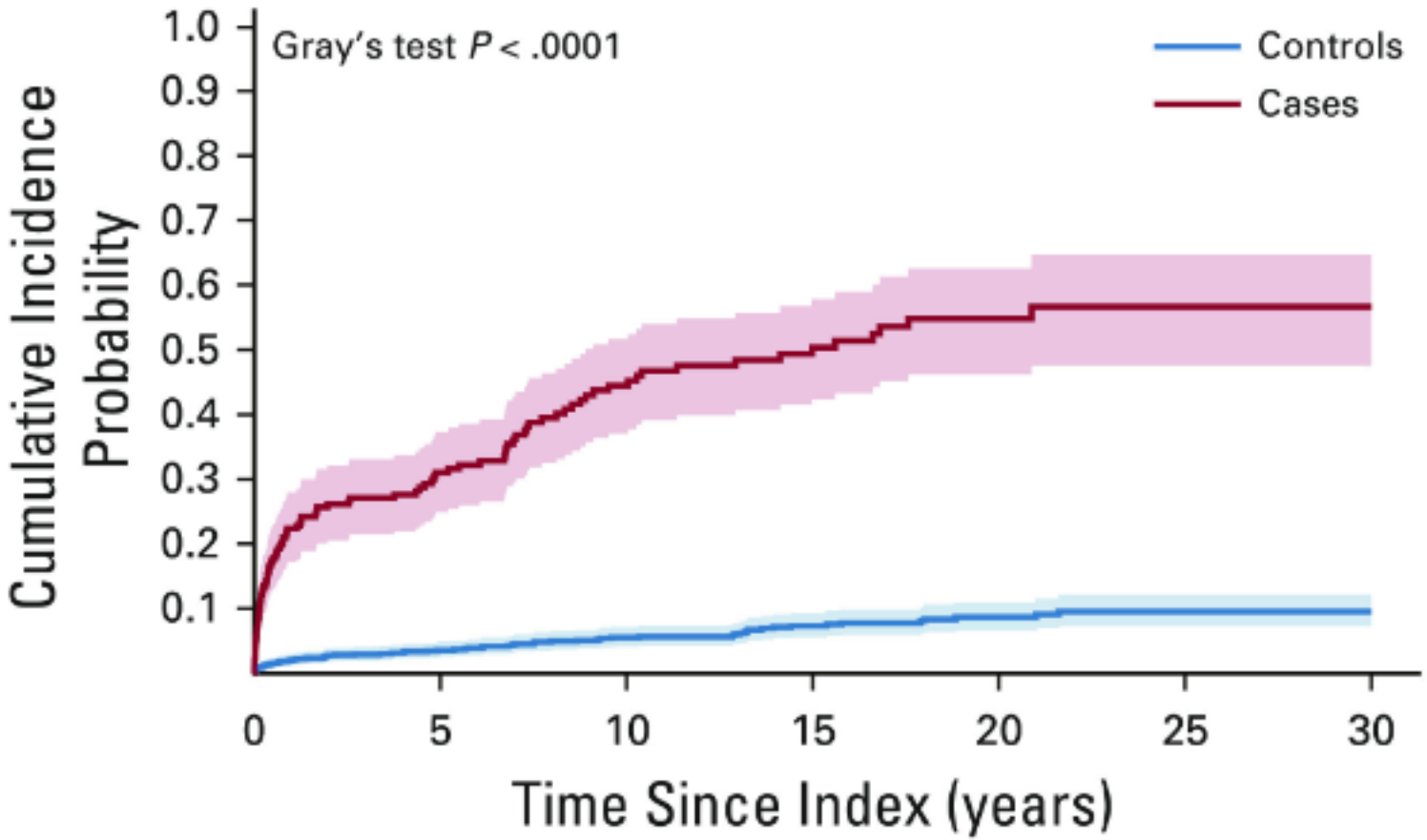
	WNT	SHH	Group 3	Group 4
	6-	3q+, 9q-, 10q-	7+, 1q+, 17q+, 18q+, 11p-, 8-, 5q-, 10q-, 16q-	7+, 17q+, 18q+, 11p-, X-, 8-
	CTNNB1 mutation	*PTCH1/SMO/SUFU* mutation *GLI2* amplification *MYCN* amplification	i17q *MYC* amplification	i17q *CDK6* amplification *MYCN* amplification

GENE EXPRESSION



	WNT	SHH	Group 3	Group 4
	WNT signaling	SHH signaling	Photoreceptor/GABAergic	Neuronal/Glutamergic
	MYC +	*MYCN* +	*MYC* +++	minimal *MYC* / *MYCN*

~50% of MB Survivors on Long-Term Disability



No. at risk:							
Controls	1,150	877	635	441	245	87	≤ 5
Cases	230	117	68	42	20	8	≤ 5

Coltin *et al*. J Clin Oncol 2023

“Infants” are especially vulnerable – cure at what cost?

Success

- Cure
- Reintegration
- Neurological integrity
- Few/no long-term side effects

“Catastrophic success”

- Cure
- Poor/no reintegration
- Neurological deficits
- Endocrine deficit
- Obesity
- Intellectual deficit
- Etc…

Slide courtesy Dr. Eric Bouffet

Progress Against Medulloblastoma

…a timeline through the decades

Content researched by and supplied to *Brain Tumour* magazine by Dr Vijay Ramaswamy and Dr Eric Bouffet, The Hospital for Sick Children (SickKids), Toronto, Canada;
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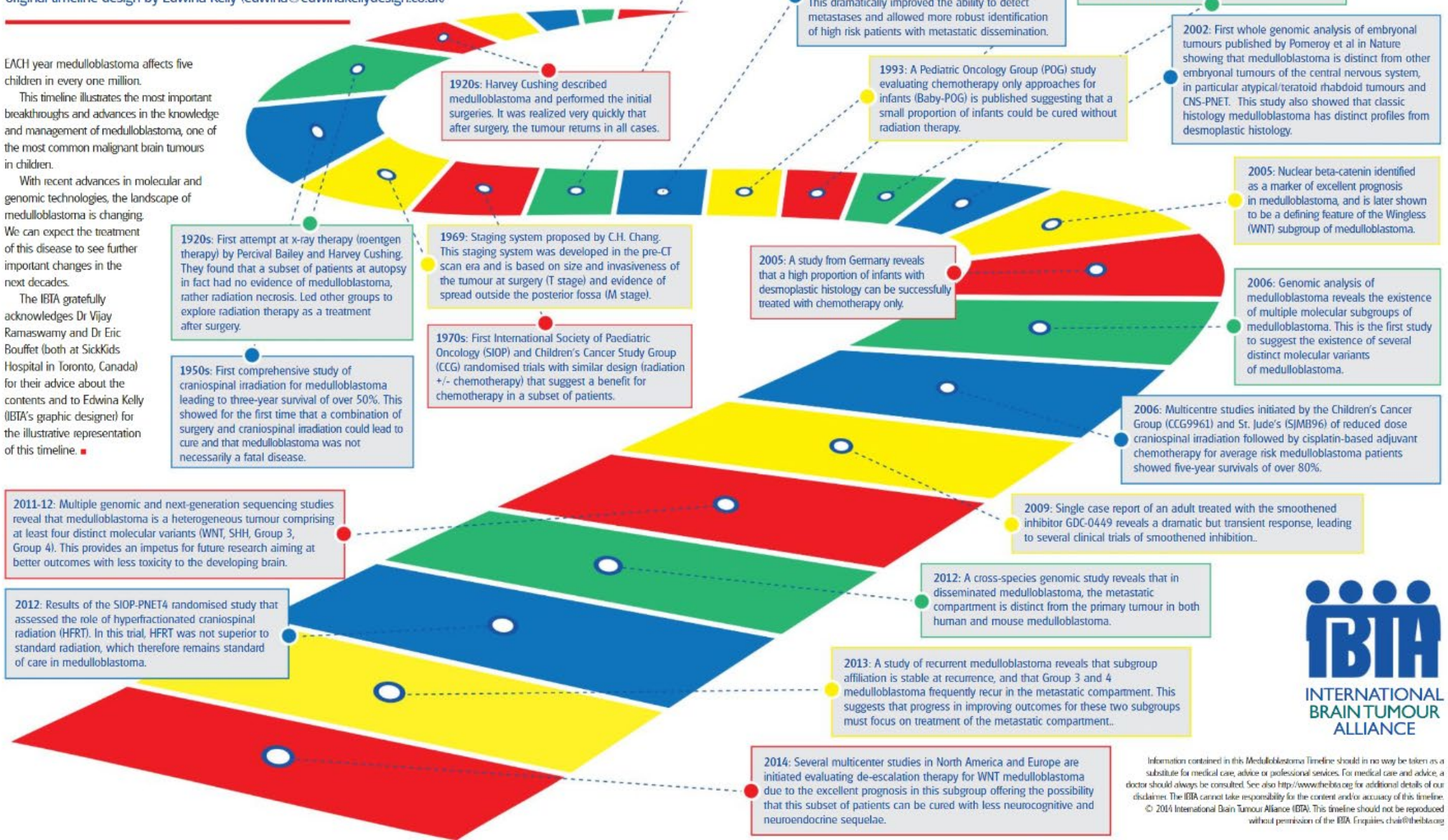

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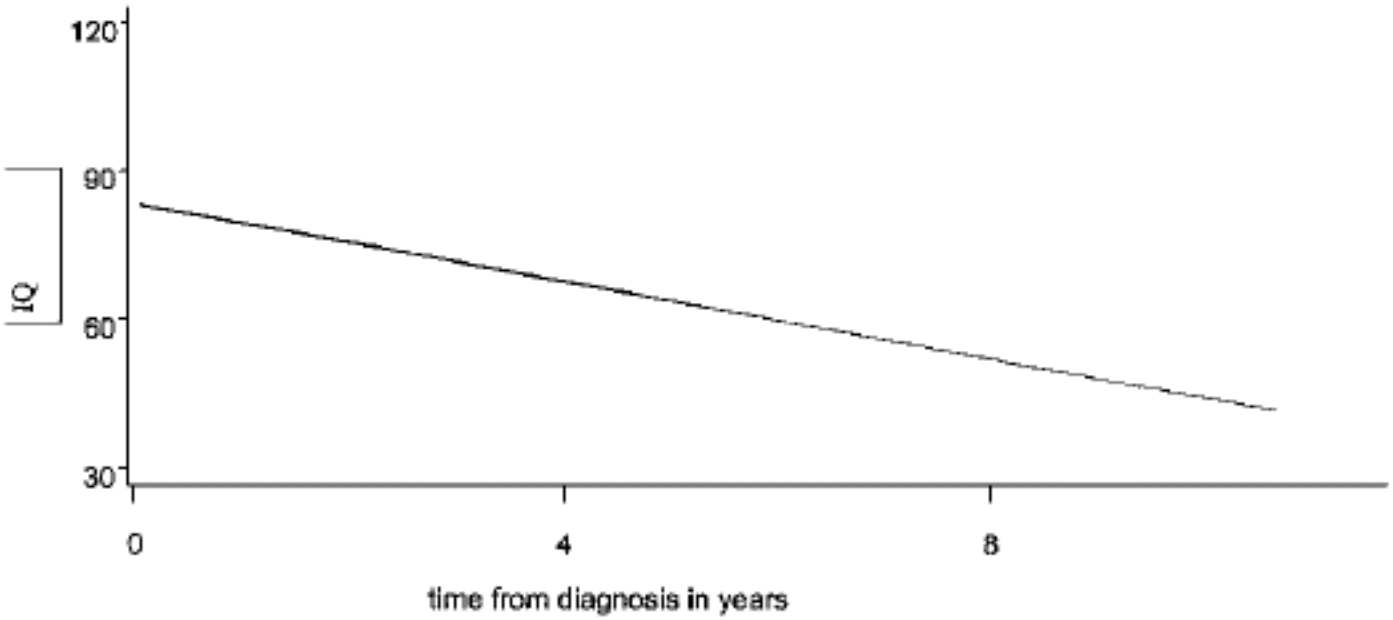
INTERNATIONAL BRAIN TUMOUR ALLIANCE

“Infants” are especially vulnerable



Neurodevelopmental Outcome

Neurodevelopmental assessments are reported only for children who survived ≥ 24 months from diagnosis (n = 19) so that meaningful conclusions can be drawn about survivors. All 19 subjects had ≥ two evaluations; a total of 65 test observations formed the basis for the neurodevelopmental analysis. Children lost significant cognitive function, as measured by IQ scores, during and after therapy (P = .0028). The median baseline IQ value was 88 (range, 50 to 111), compared with 62 (range, 44 to 86) at our most recent follow-up evaluation, a median of 4.8 years (range, 2 to 10.6 years) after diagnosis. The rate of decline during this interval (Fig 4) was 3.9 IQ points per year (95% confidence interval, 1.12 to 5.60; P = .0028). Cognitive losses do not yet seem to have reached a plateau. At the most recent evaluation, all children were receiving special educational services.

Median age at radiation:
M0 patients: 2.9 years (1.3-5.3)
M+ patients: 3.3 years (2.1-5.1)

Walter *et al*. J Clin Oncol 1999

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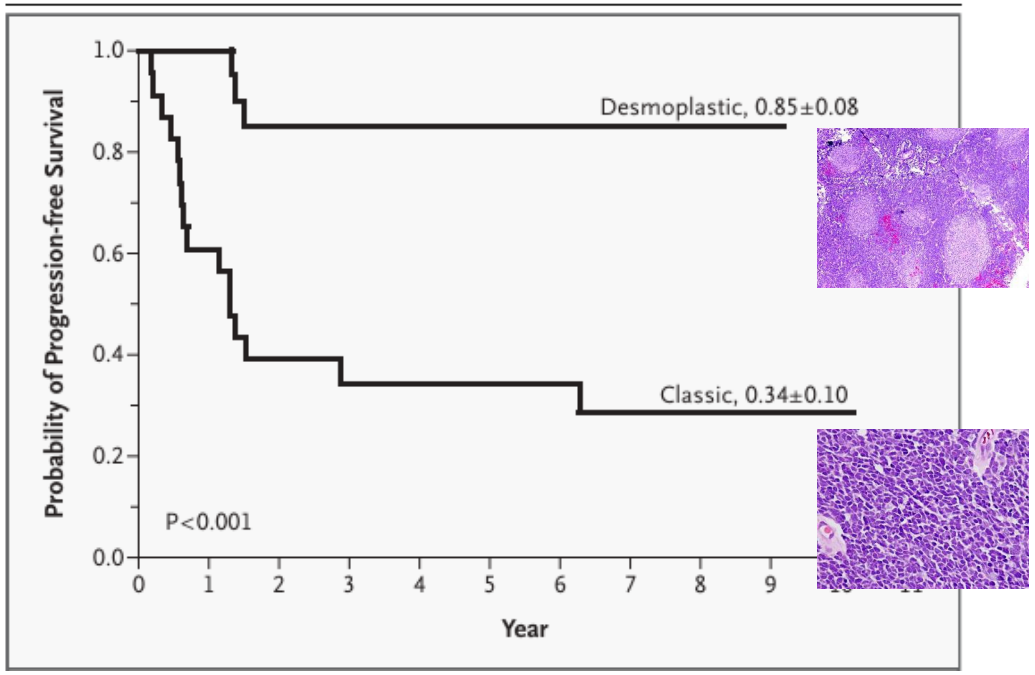
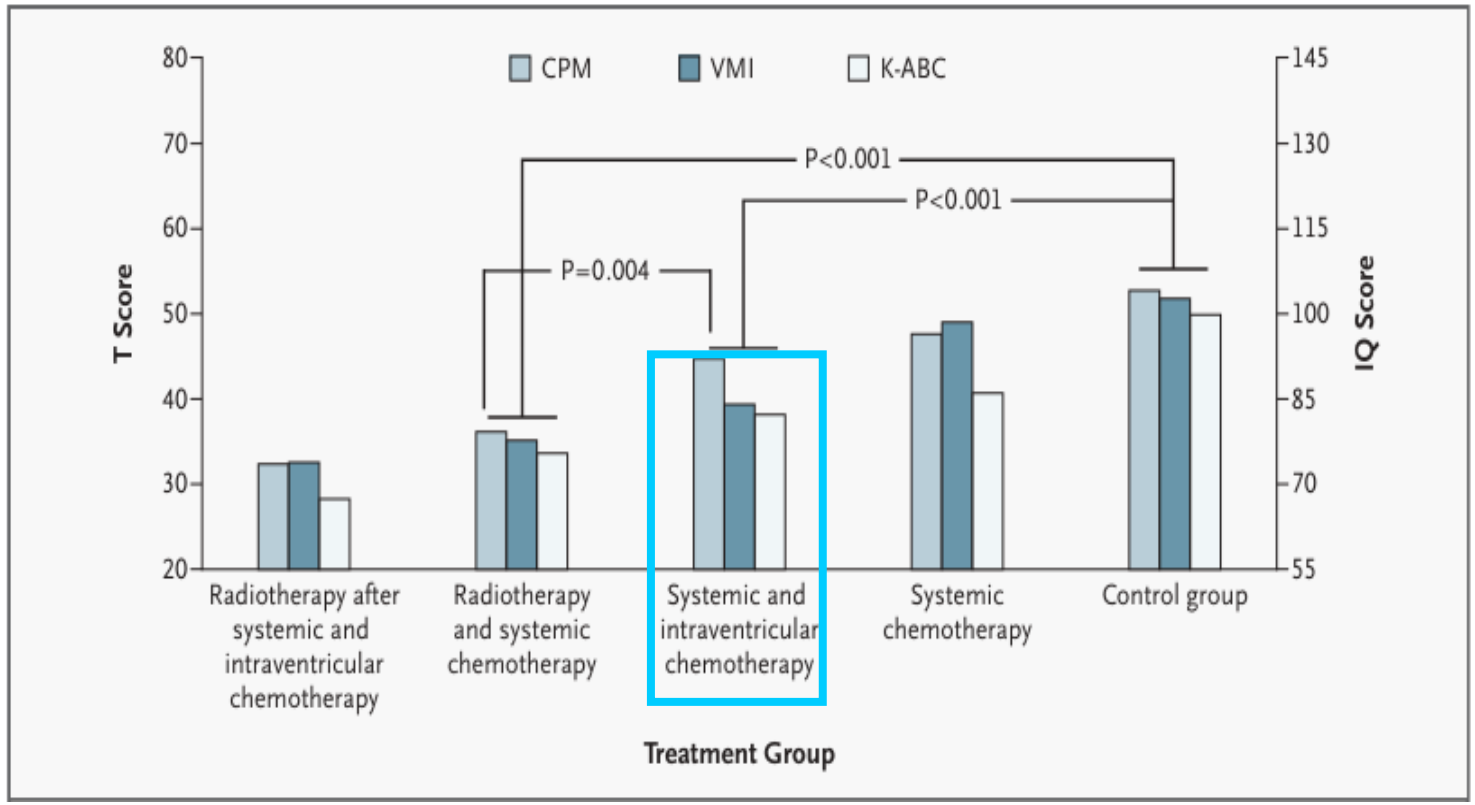
INTERNATIONAL BRAIN TUMOUR ALLIANCE

Radiation avoidance in young children with MB associated with improved neurocognitive outcome

Table 1. Chemotherapy Regimen.*

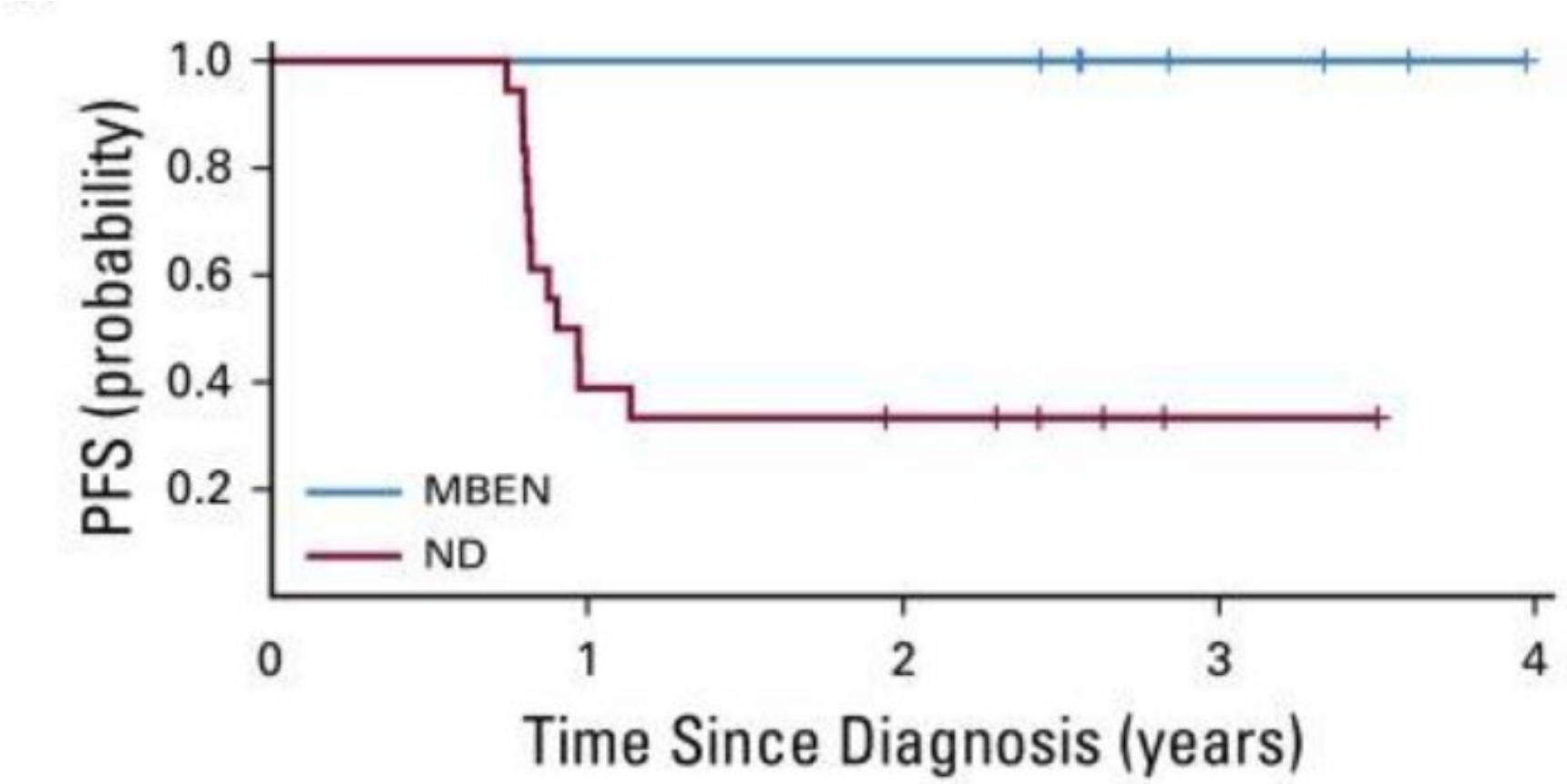
Week 1	Week 3	Week 5	Week 7
Methotrexate (2 mg/day, intraventricular), day 1–4	Methotrexate (2 mg/day, intraventricular), day 1–2	Methotrexate (2 mg/day, intraventricular), day 1–2	Methotrexate (2 mg/day, intraventricular), day 1–4
Cyclophosphamide (800 mg/m² of body-surface area/day, intravenous), day 1–3	Methotrexate (5 g/m², intravenous), 24 hr	Methotrexate (5 g/m², intravenous), 24 hr	Carboplatin (200 mg/m², intravenous), day 1–3
Vincristine (1.5 mg/m², intravenous), day 1	Vincristine (1.5 mg/m², intravenous), day 1	Vincristine (1.5 mg/m², intravenous), day 1	Etoposide (150 mg/m², intravenous), day 1–3





Rutkowski *et al*. N Engl J Med 2005

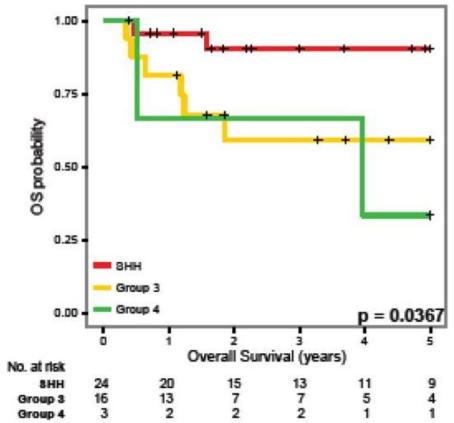
Intraventricular methotrexate can be avoided for small subset of SHH MB



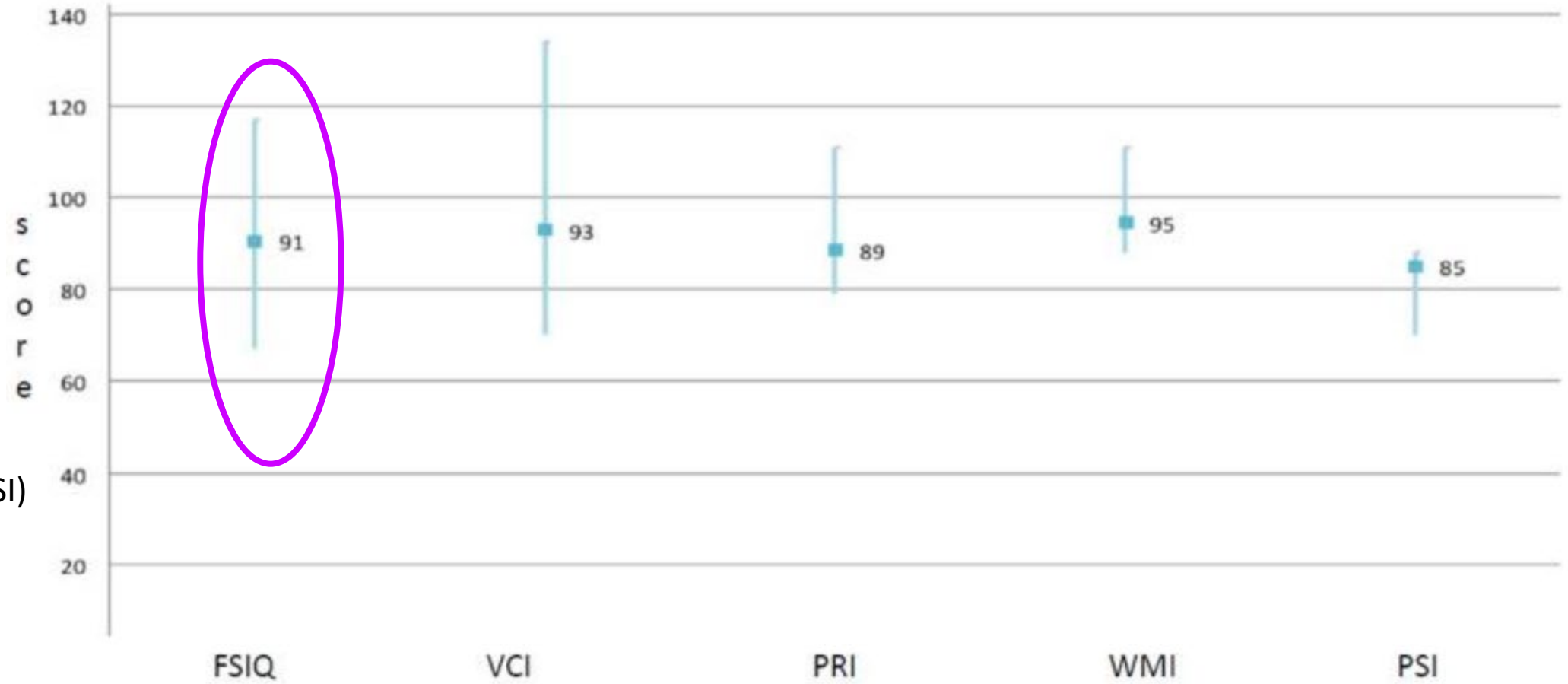
No. at risk:					
MBEN	7	7	7	3	0
ND	18	7	5	1	0

Lafay-Cousin *et al*. J Clin Oncol 2020

Radiation-sparing approach associated with cure for SHH and normal IQ scores



- 17 pts radiated
- 9 upfront (6 focal, 3 CSI)



Lafay-Cousin *et al*. Pediatr Blood Cancer 2016

Infantile MB Summary

- Cure is possible with radiation-sparing approach, largely for SHH-MB
- Radiation avoidance associated with improved neurocognitive outcomes
- Definition of “infants” shifted over time - <5 y/o in Toronto

What about older kids?

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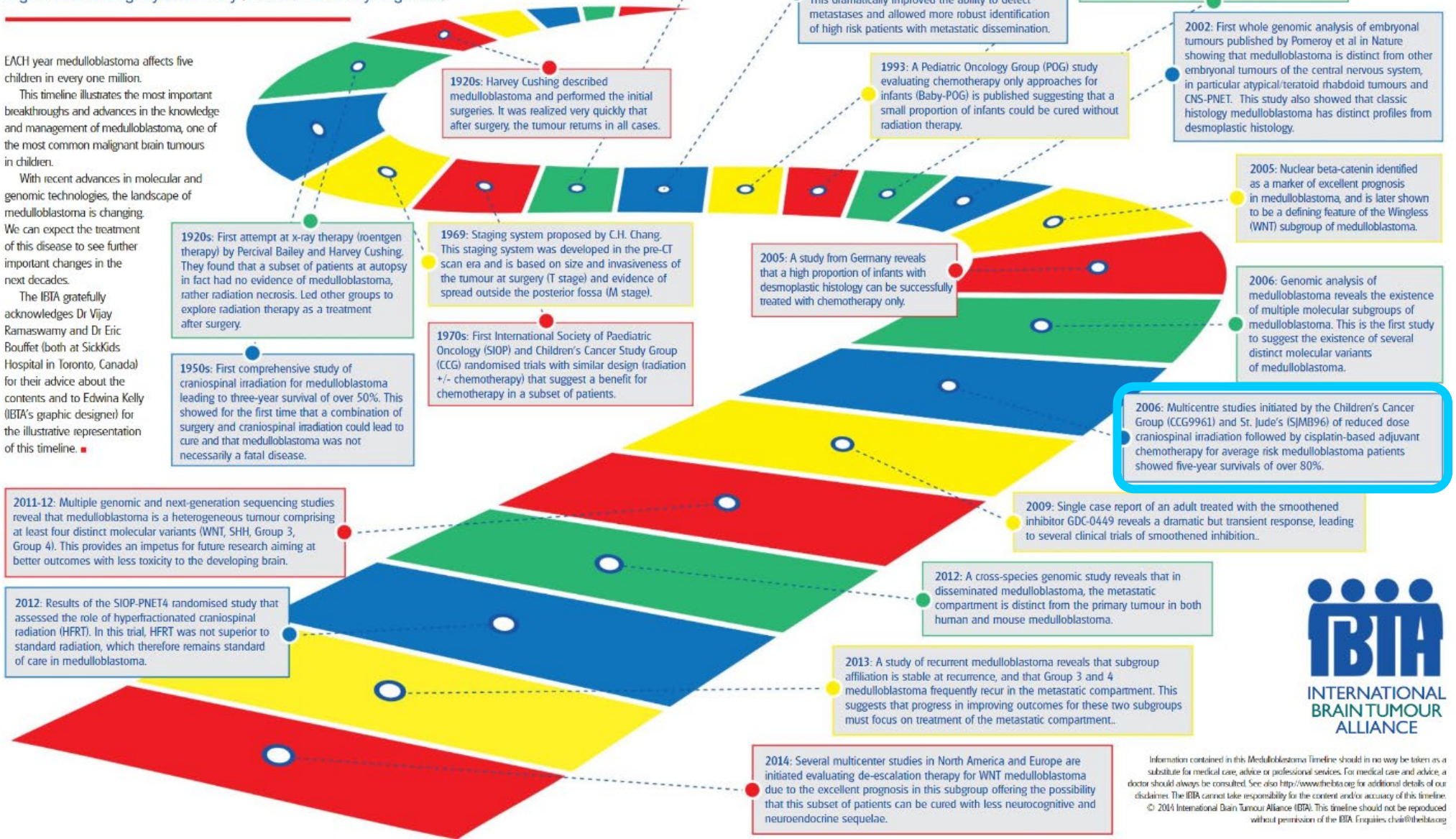

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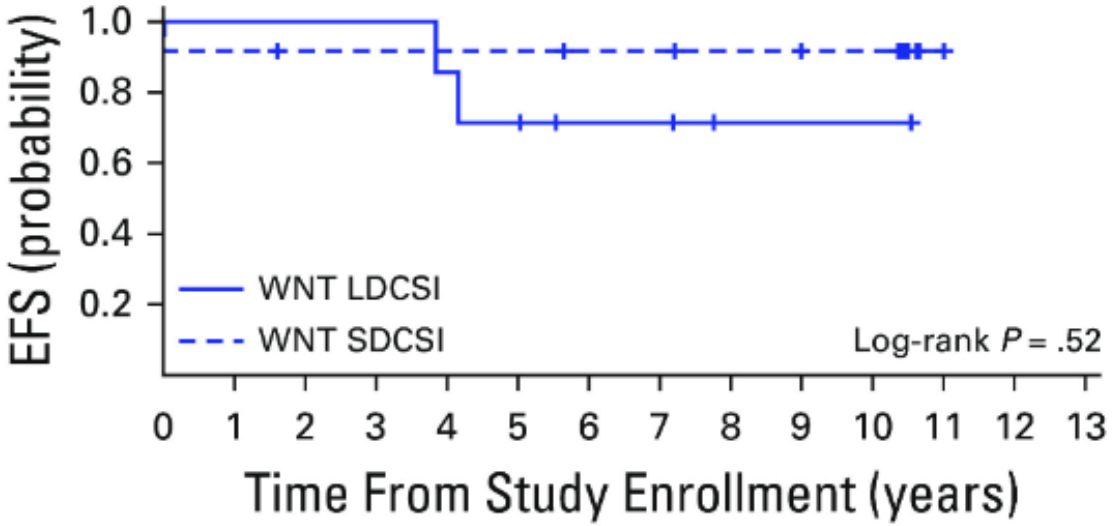
Average Risk – 23.4 Gy CSI

High Risk – 36 Gy CSI

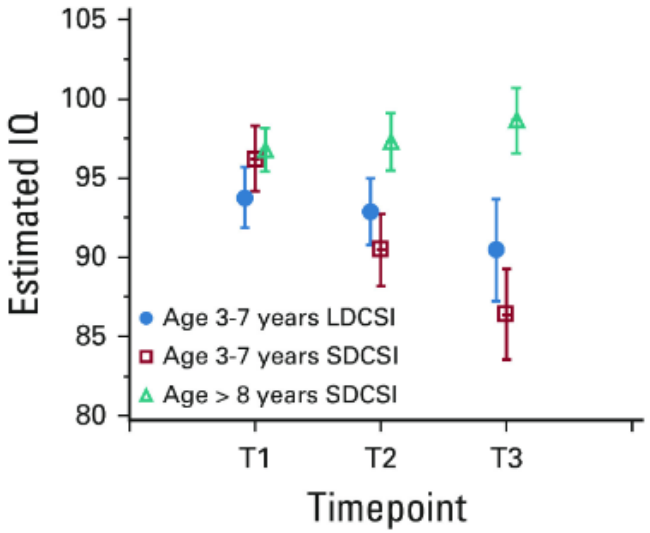
Can we reduce this further??

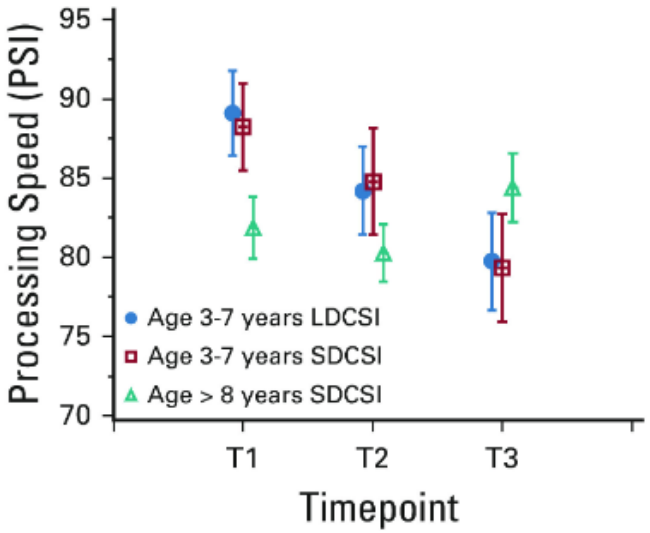
18 Gy CSI maintains outcomes for AR WNT MB
→ Ongoing trials with 18 Gy (COG) and 15 Gy (SJ)



No. at risk:

LDCSI	7	7	7	7	6	5	3	3	1	1	1	0	0	0
SDCSI	12	11	10	10	10	10	9	9	8	7	7	1	0	0

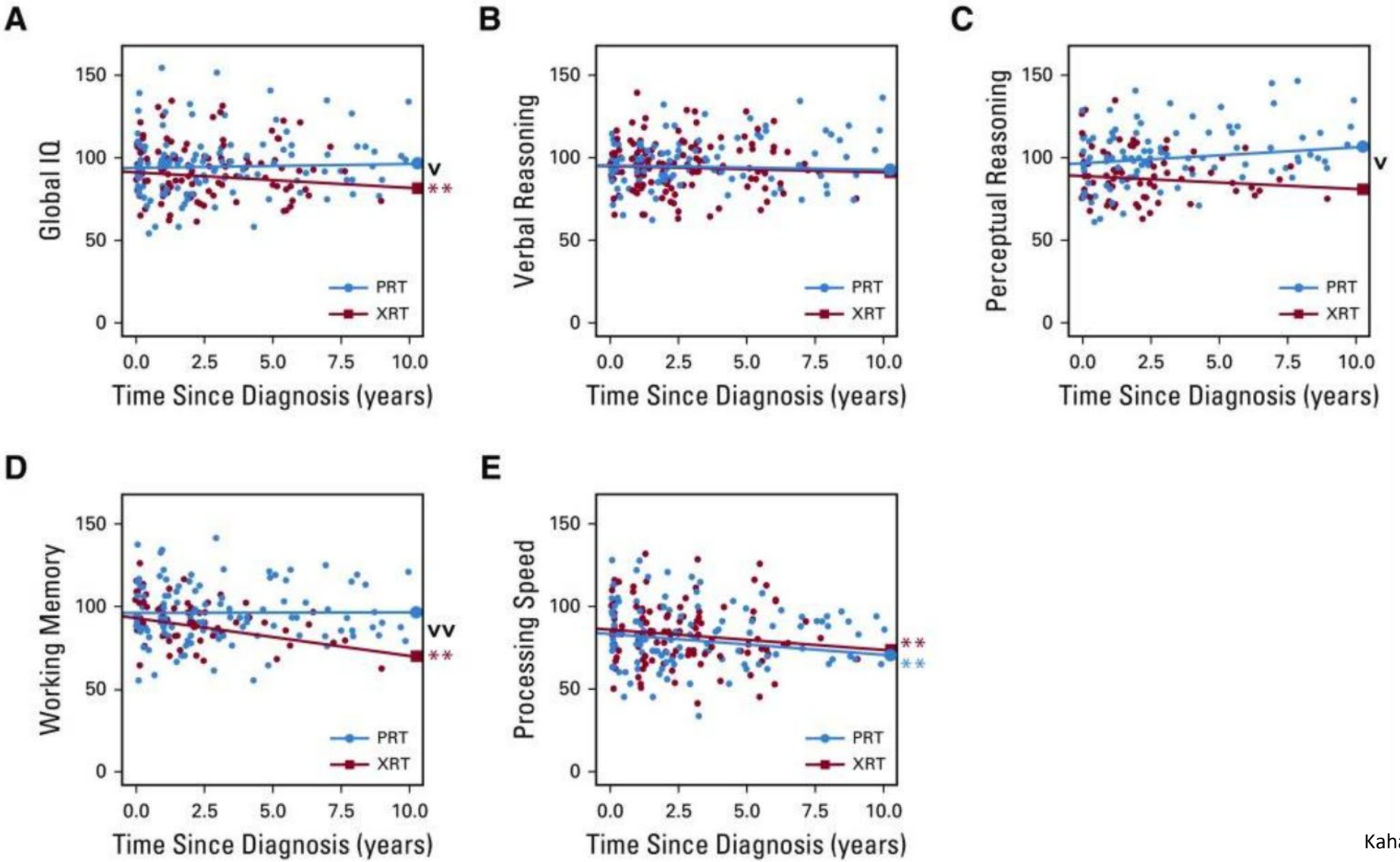




Michalski *et al*. J Clin Oncol 2021

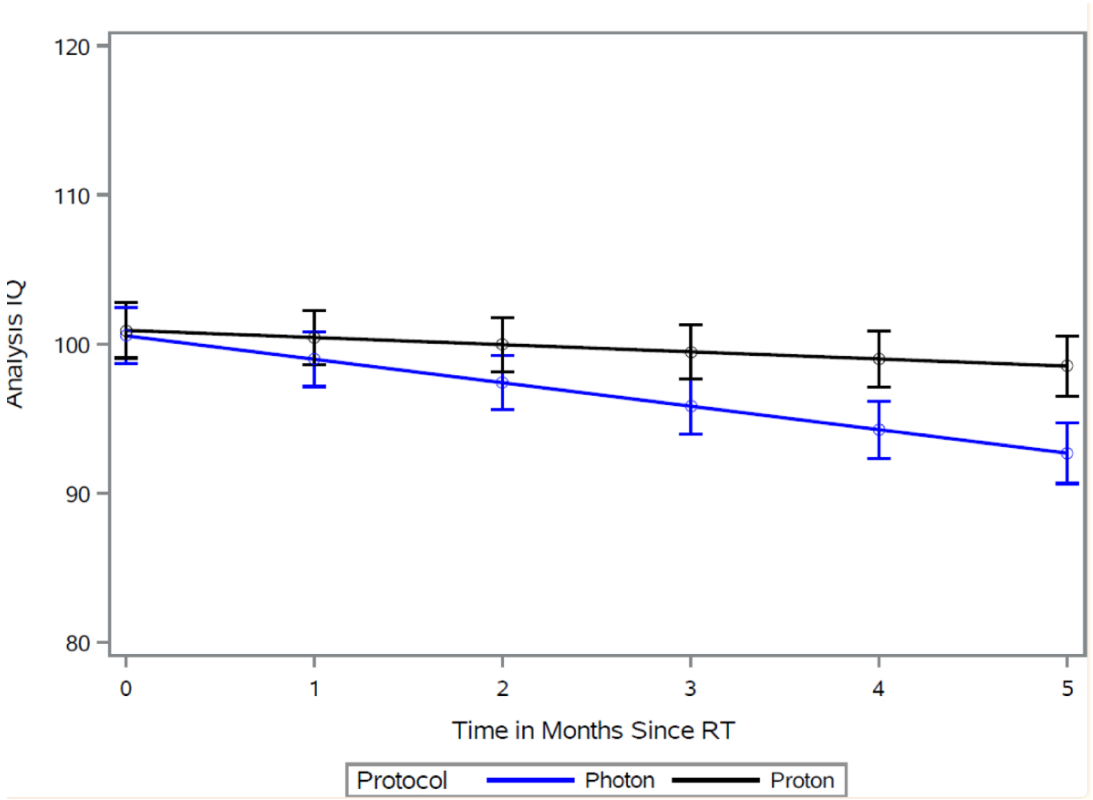
Does the type of radiation matter?

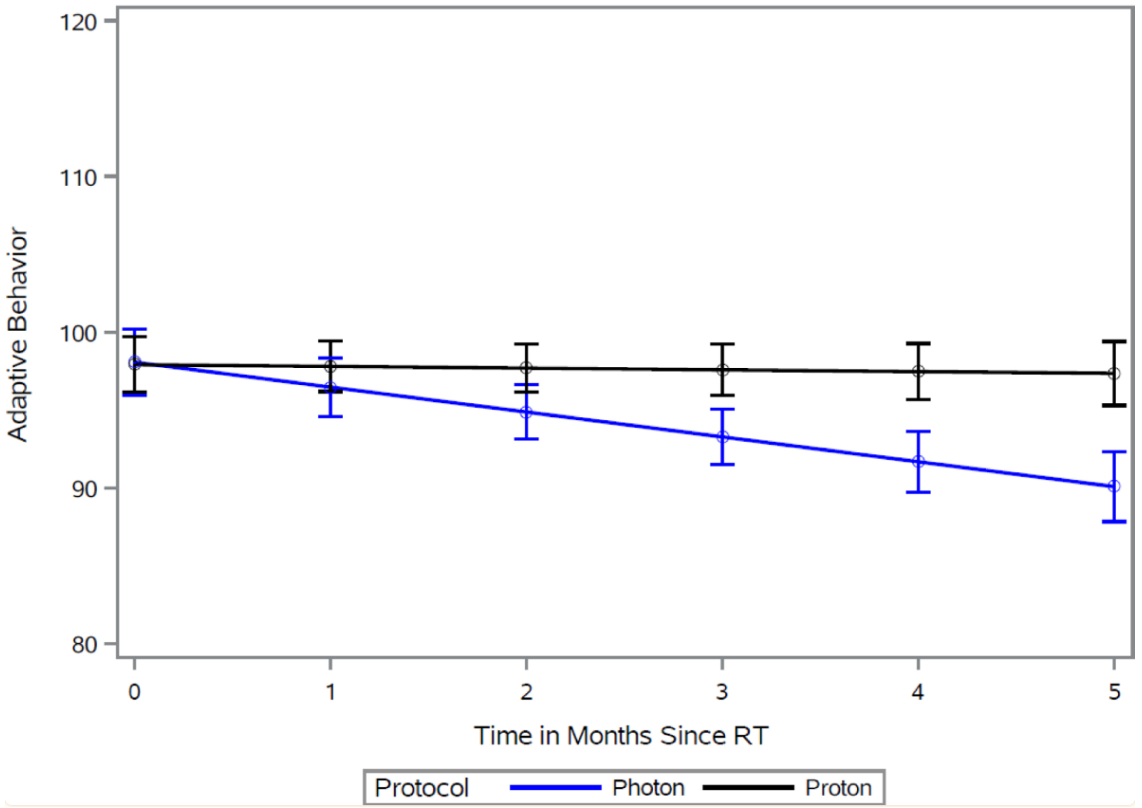
Improved neurocognitive outcomes in MB treated with protons



Kahalley *et al*. J Clin Oncol 2020

Benefit of protons on neurocognition replicated in craniopharyngioma (focal RT)

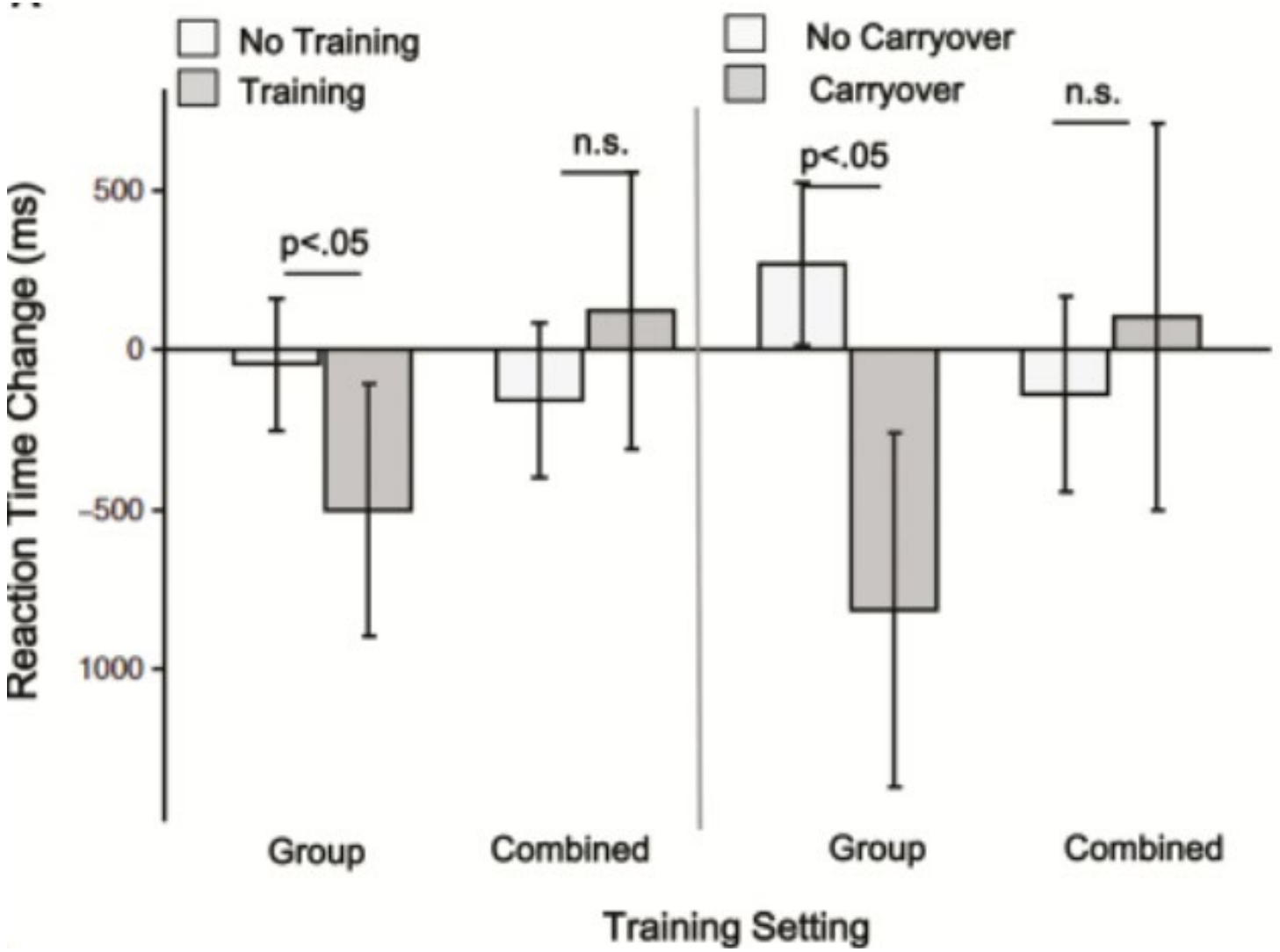


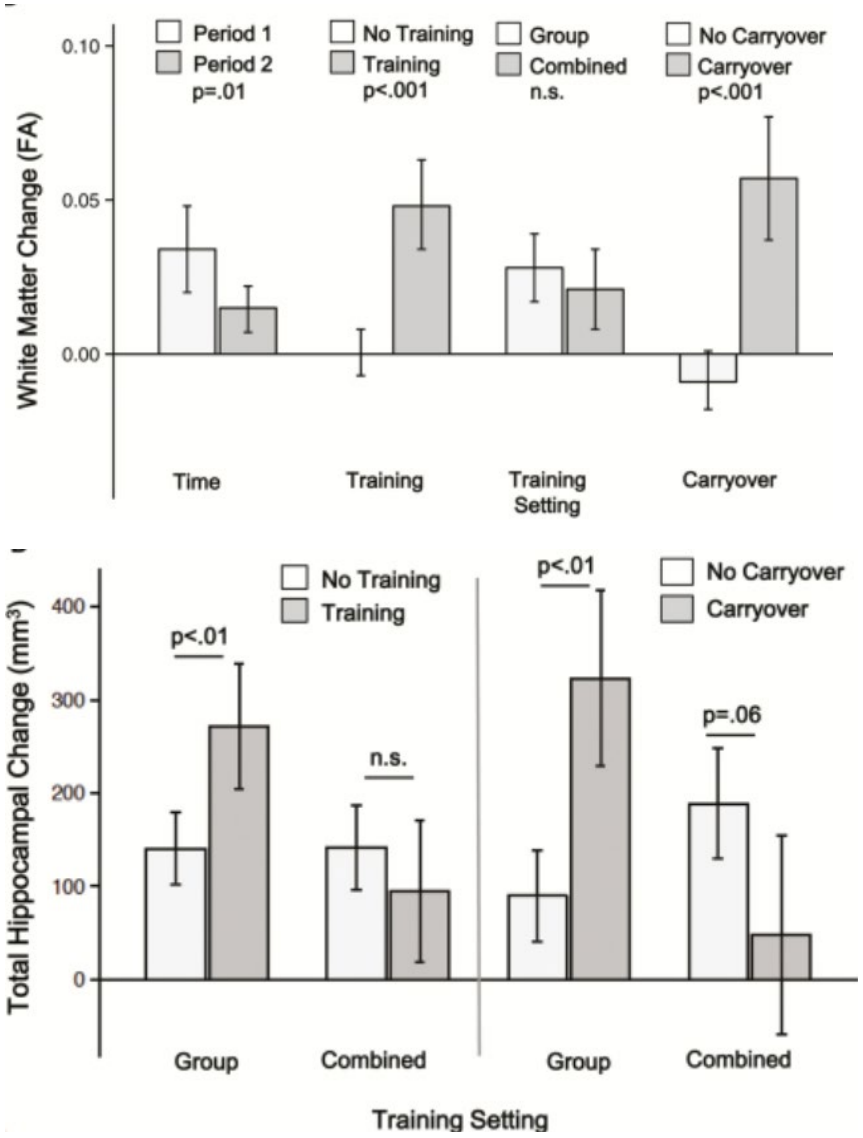


Merchant *et al*. Lancet Oncol 2023

Intervention following End of Therapy

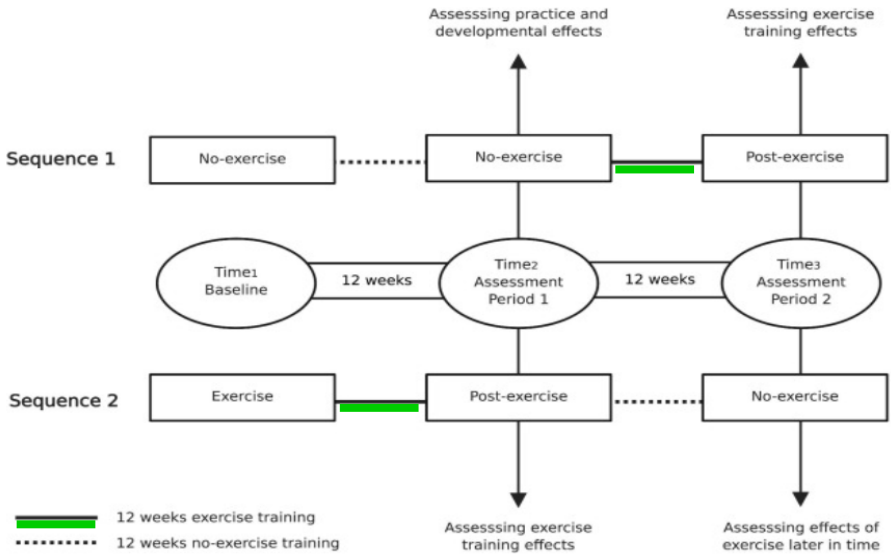
12 week exercise program improved reaction time in MB survivors



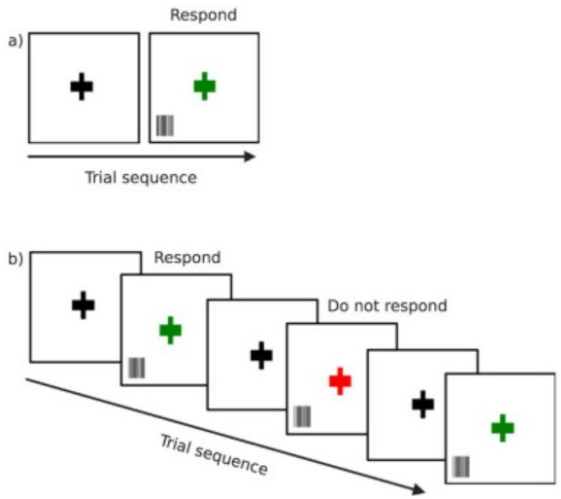


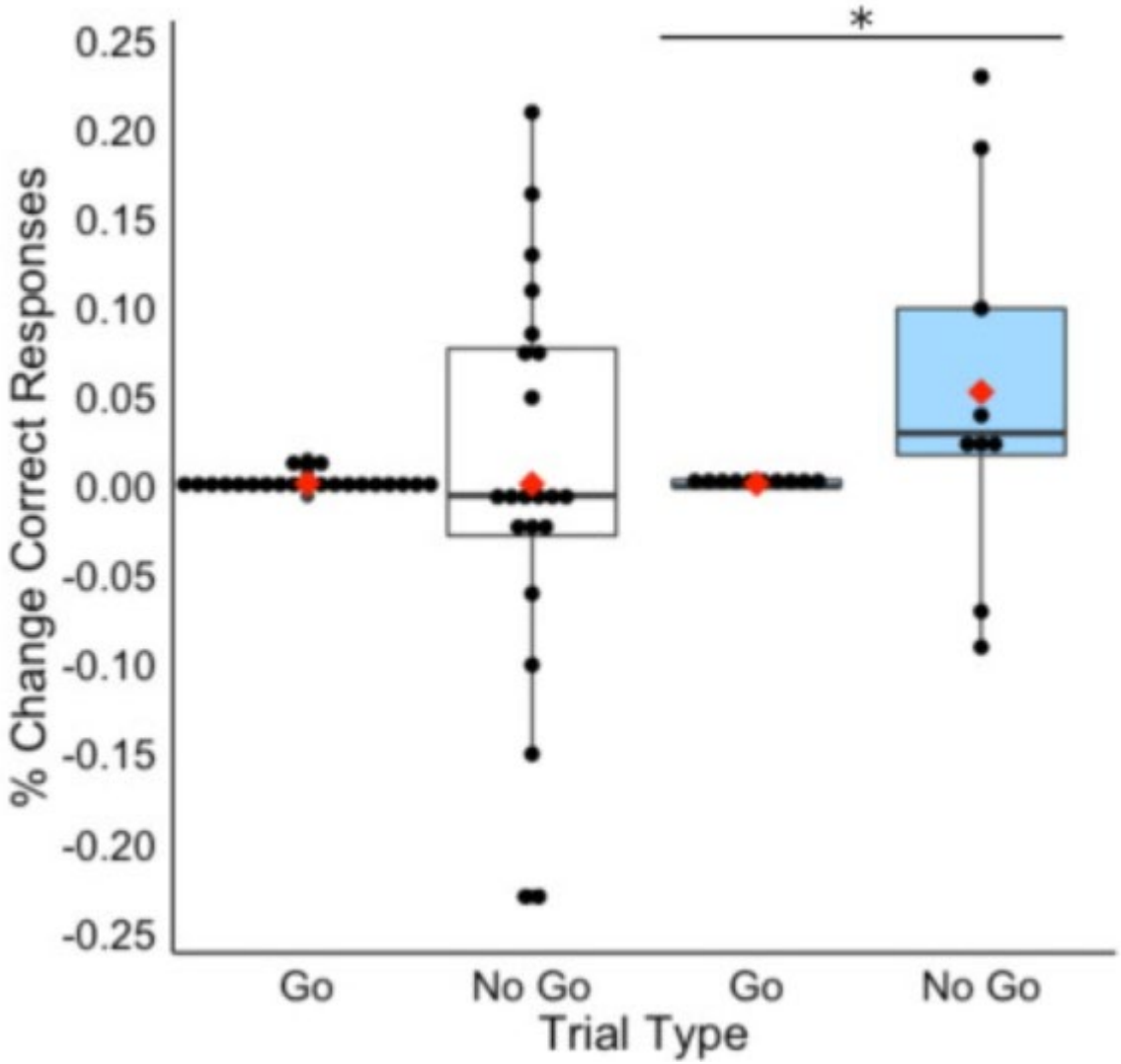
Riggs *et al*. Neuro Oncol 2017

Exercise may promote cognitive recovery in brain tumor survivors



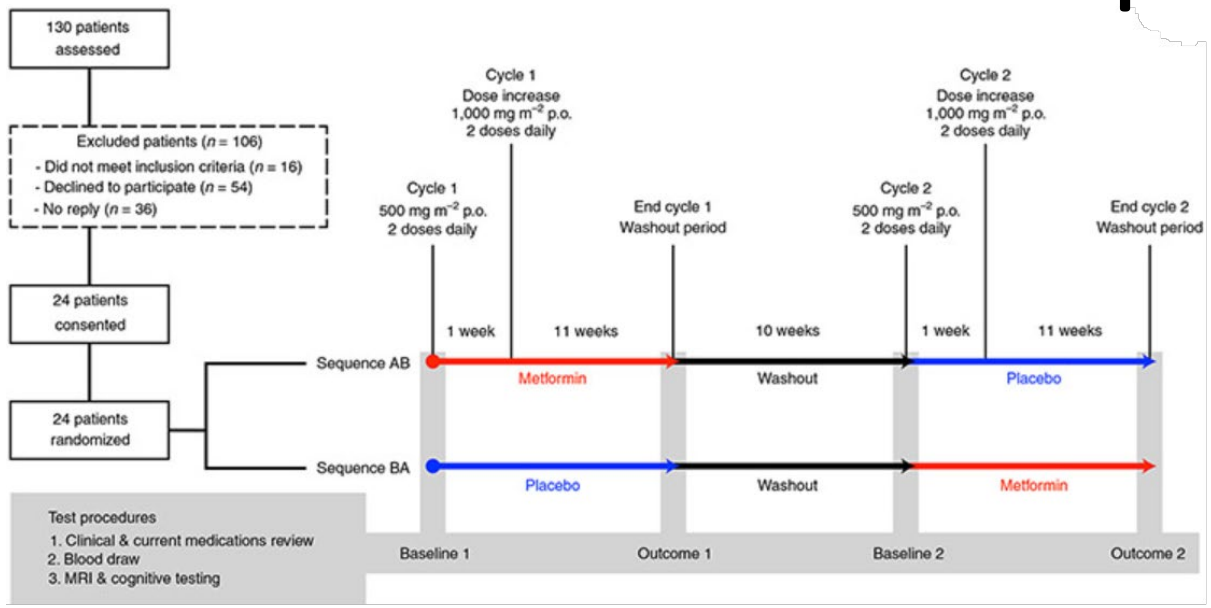
MEG

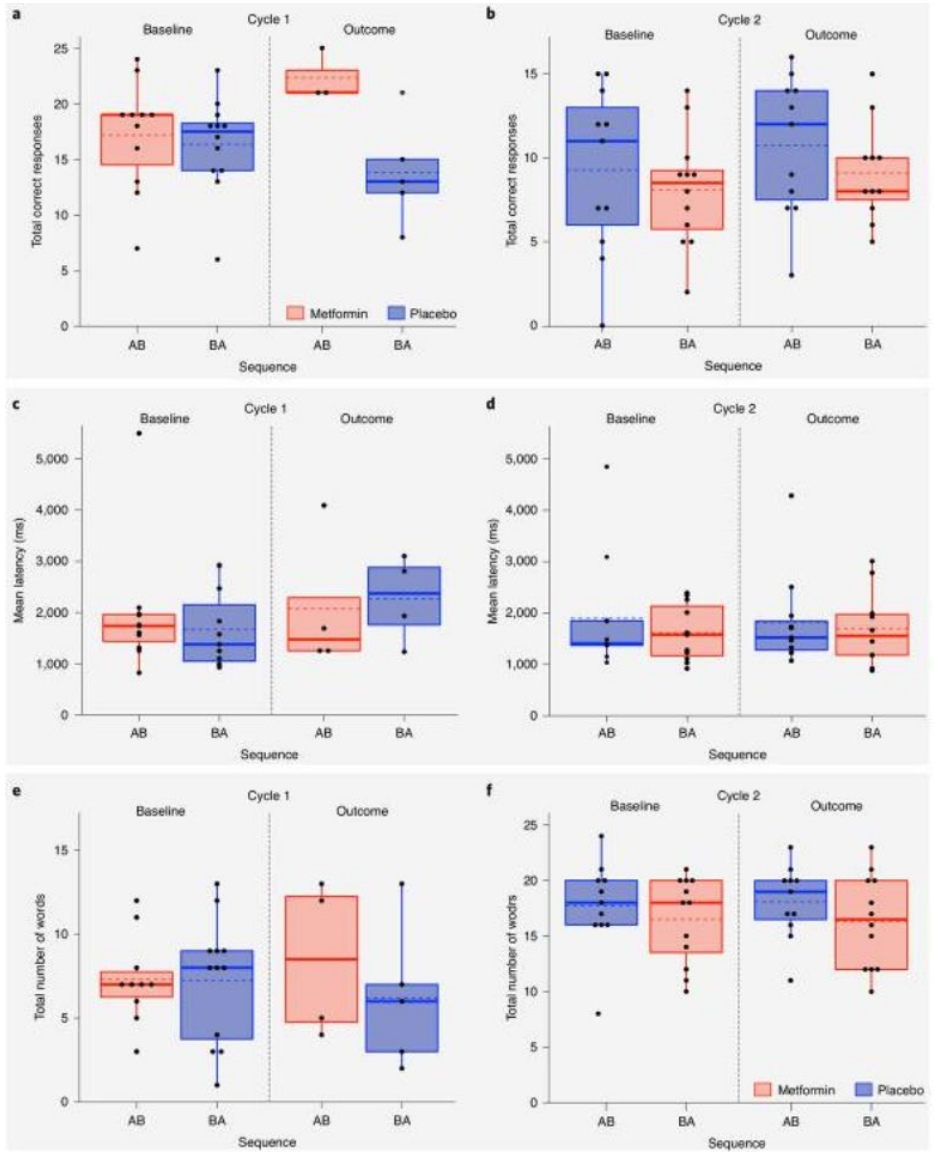


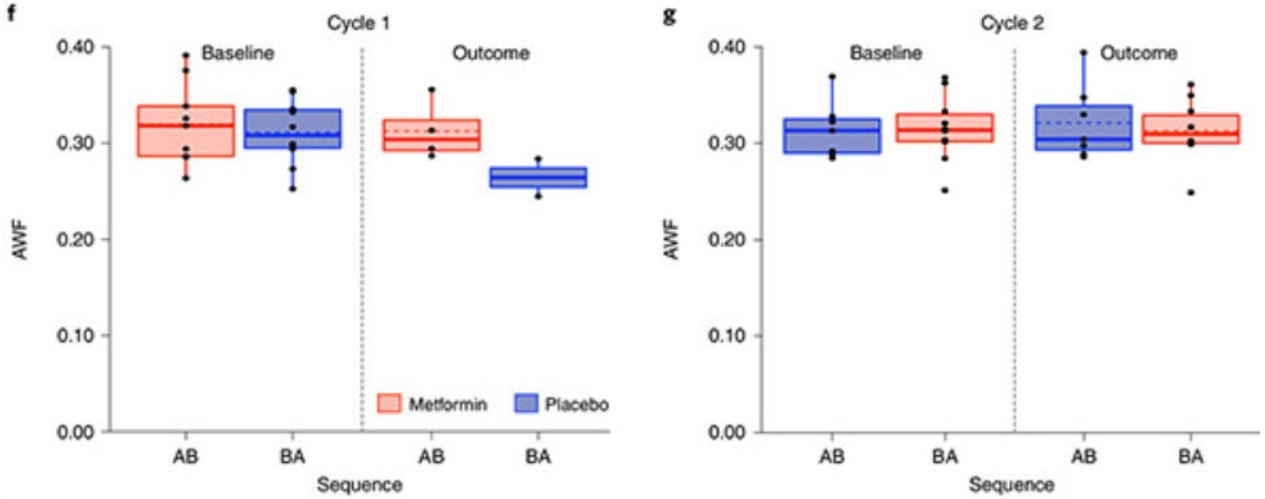


Cox *et al*. Clin Neurophysiol 2020

Metformin safe and encouraging results in pilot trial → phase 3 trial







Ayoub *et al*. Nat Med, 2020

Conclusions

- Neurocognitive deficits are a major issue in the care of CNS tumor survivors
- Better understanding of tumor biology and use of newer treatment modalities can deliver tailored therapy resulting in reduced risk to neurocognition
- Novel therapies introduced after end of cancer treatment are currently being studied to improve neurocognitive outcomes

Questions?