Quality of Survival
after CNS tumours in childhood

Colin Kennedy

AIMS OF
NEURO-ONCOLOGY

ALTER THERAPY

↑ **SURVIVAL**   ↑ **QUALITY OF LIFE**
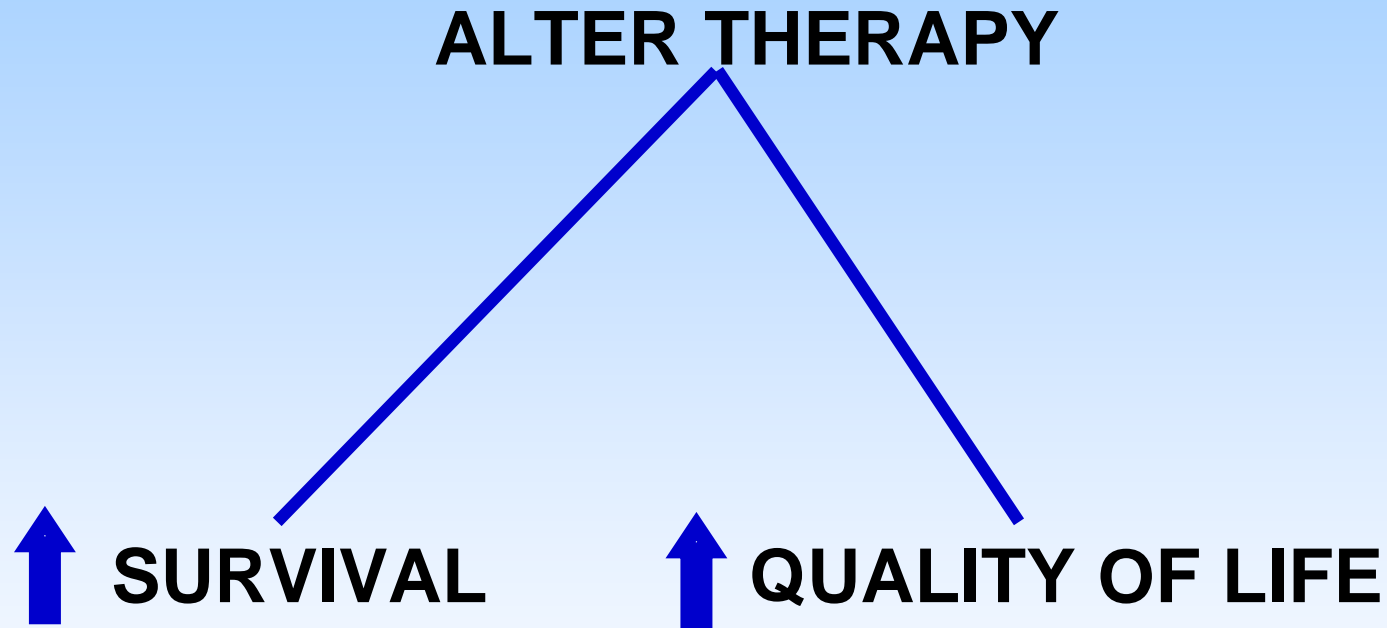
Quality of survival after childhood brain tumours

- The big picture

- Illustrations in posterior fossa tumours

  - Chemotherapy
  - Variations on radiotherapy
  - Psychosocial factors
  - Surgery
  - Current work with on-line tools

the big picture

Socio-demographic Outcomes

	Survivors % (n=2,821)	Sibs %	Odds Ratio (95%CI)*
High School Grad.	91	99	3.7 (2.5-5.5)
Married	33	69	4.3 (3.7-5.1)
Employed	67	94	12.0 (9.1-15.8)
Income >20,000	76	93	3.7 (2.9-4.8)
Insured	88	91	1.1 (.8-1.4)

5 yr survivors of CNS tumours diagnosed in 1970- 1986

* Adjusted for age, sex and intra-family correlation

Armstrong et al, JNCI 2009, 101: 946

Health Impairment

	Survivors %	Sibs %	Odds Ratio (95%CI)*
General Health	53	17	22.5 (14.3-35.3)
Mental Health	21	14	1.4 (1.2-1.7)
Functional Status	38	3	25.9 (18.9-35.4)
Activity Level	19	0.6	39.5 (22.7-68.7)
Pain	10	1	7.6 (4.9-11.8)
Anxiety	8	1	10.0 (6.2-16.2)

*Adjusted for age at interview, sex, ethnicity, education, income and health insurance

Armstrong et al, JNCI 2009, 101: 946

Chronic Health Conditions: New onset after 5 years

	Cumulative Incidence (%)	Rate Ratio (95% CI)
Endocrine (any)	32.2	19.8 (14.5-27.1)
-GH deficiency	23.1	140.4 (51.3-384.1)
-Hypothyroidism	19.0	13.0 (9.2-18.3)
Musculoskeletal	7.3	13.8 (7.4-25.7)
Neurological (any)	72.4	5.6 (4.8-6.7)
-Seizure	32.9	15.1 (10.7-21.2)
-Balance	51.6	18.0 (13.4-24.1)
- Blindness	15.5	7.5 (4.1-13.5)

Second Neoplasms by RT dose

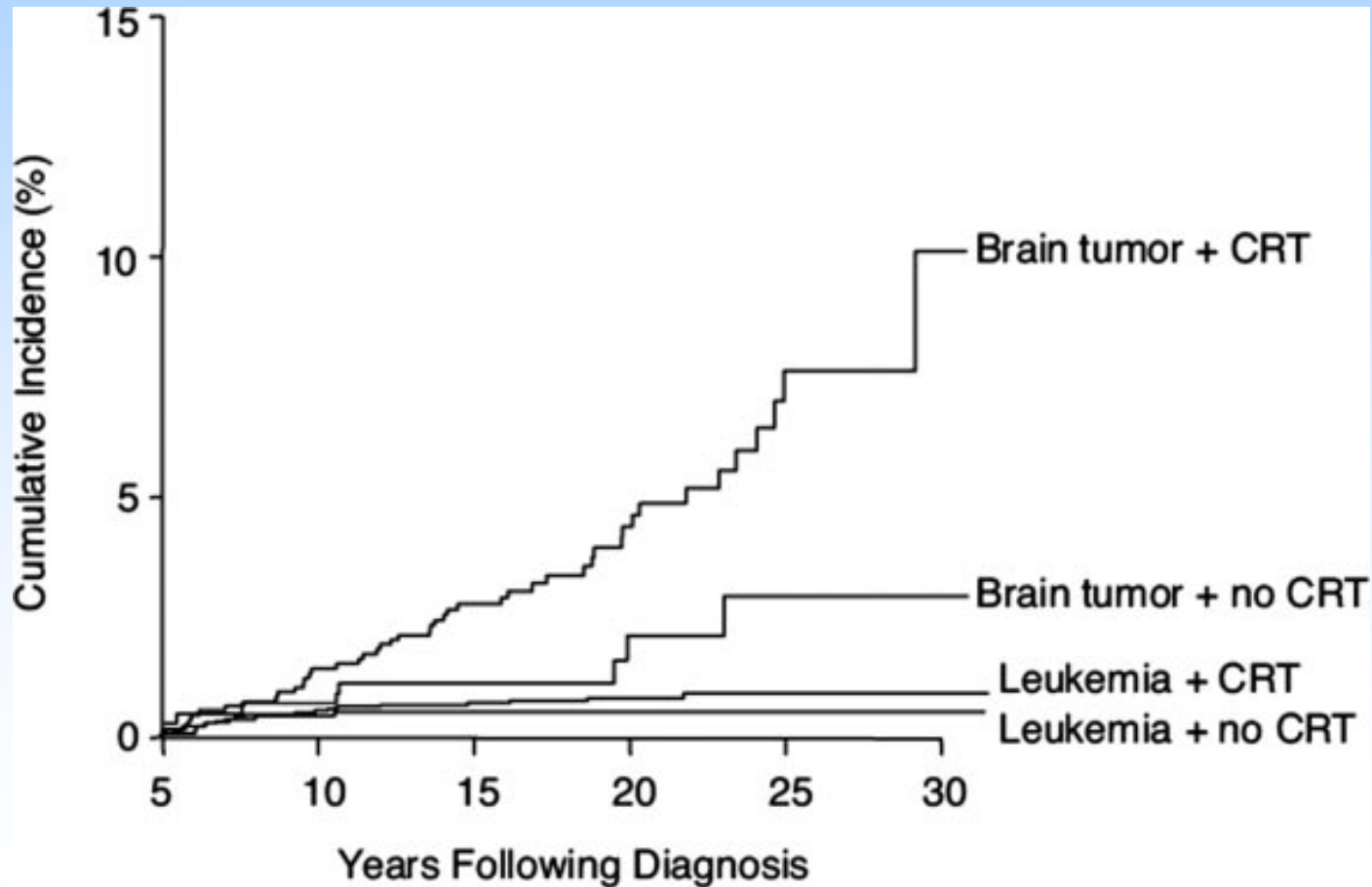Armstrong et al, JNCI 2009, 101: 946
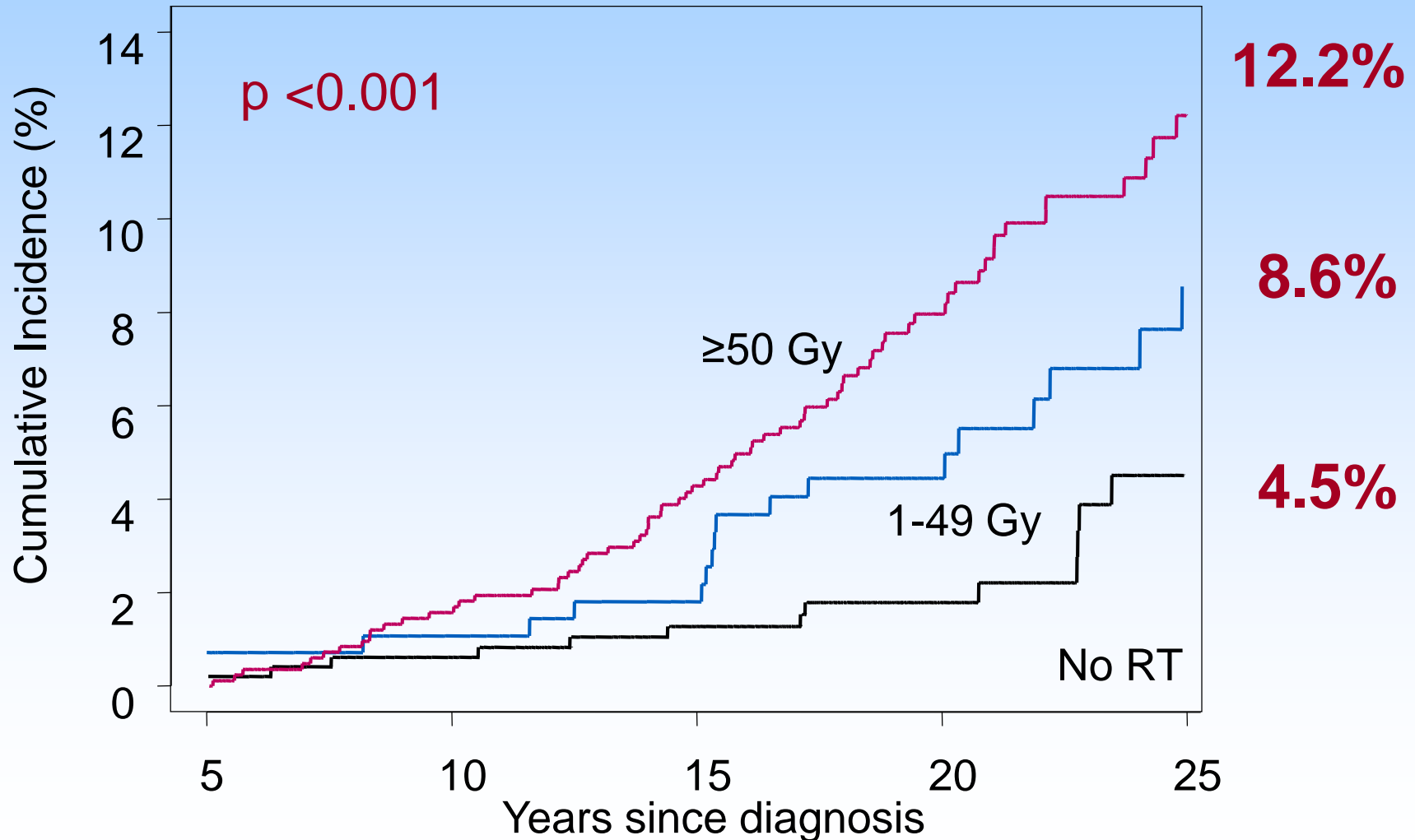
occurrence of late-occurring stroke among brain tumor survivors

Clinical sequelae
small v.: Mineralizing microangiopathy; impaired vasovasorum; possible brain necrosis
medium and large v.: stenosis; aneurysm;vascular malformation

risk factor: radiation

very well known dose- and volume- related risks, especially in younger patients

risk factor: location

- Cerebral hemisphere – high risk for cognition
- Midline – high risk, especially third ventricle
- Posterior fossa – lower risk but includes cognitive risks

risk factor: hydrocephalus

- in some studies only

but ……
not all late effects are due to radiation
see good review by Duffner EJPN 2010, 14, 106

1986-2010: treatment modification
to reduce risk factors

- **reduce volume and dose radiation**
- **↑↑↑ use chemotherapy**
  - **adjuvant with reduced dose RT**
  - **chemotherapy-only protocols**
  - **high dose chemotherapy with transplant/stem cell support**
- **new radiation techniques**
  - **Hyperfractionation**
  - **conformal RT**
  - **PBT**
- **↑ aggressive surgery**

after Duffner EJPN 2010, 14: 106

How should we measure quality of survival after childhood brain tumour?

Jennifer A. Limond [a,*], Kim S. Bull [b], Gabriele Calaminus [c], Colin R. Kennedy [b,d], Helen A. Spoudeas [e], Mathilde P. Chevignard [f,g], on behalf of the Brain Tumour Quality of Survival Group, International Society of Paediatric Oncology (Europe) (SIOP-E)
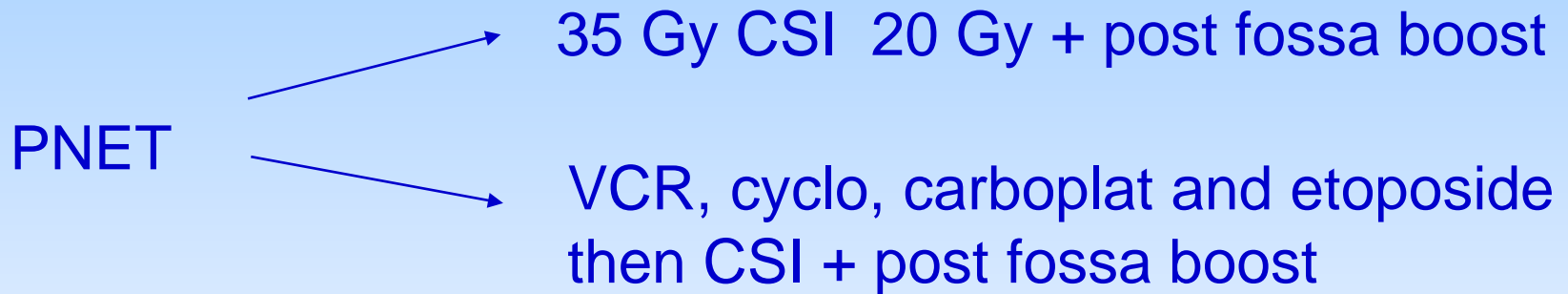
1. Background
   a. Survivorship after childhood brain tumour
   b. Terminology and conceptual framework
2. Developing an Agreed Protocol
3. Domains and Measures
   a. Direct Assessment: 'Core Plus'
   Table of Core and Supplementary ('Plus') Domains for Direct Assessment
   b. Indirect Assessment
3. Measurement of Endocrine Outcomes
4. Individuals with Sensory Impairments
5. Implementing an agreed protocol in European trials

Cerebellar tumours
as an example

1. **chemotherapy: the low toxicity alternative?**

chemotherapy

PNET3 outcome study for medulloblastoma

35 Gy CSI 20 Gy + post fossa boost

PNET

VCR, cyclo, carboplat and etoposide
then CSI + post fossa boost

3 year survival 78.7 vs 64.2 % (randomised patients)

Outcomes :

- neurological function   - health status (HUI3)
- educational provision   - behaviour (SDQ)
- quality of life (PedsQL, CHQ-PF28)

A UK CCL group study
Funded by The Brain Tumour Charity

characteristics of 127 ascertained children

(73% of all eligible UK children)

		CSI + chemo n=60	CSI n=67
age at diagnosis (yrs)	mean (SD)	9 (4)	8 (3)
	range	3 – 18	3 – 15
years from diagnosis	mean (SD)	7 (2)	7 (2)
	range	3 – 12	3 – 11
age at assessment (yrs)	mean (SD)	16 (4)	16 (4)
	range	8 – 24	7 – 24
male to female (%)		63 to 37	67 to 33
peri-operative complications (%)		58%	38%

functional neurological outcome (%)

	CSI + chemo	CSI
info from doctor/nurse (n=124)		
abnormal motor exam	53	44
bulbar problems	0	3
visual impairment	29	21
hearing impairment	12	6
anticonvulsant rx ever	12	9
info from parent/self (n=119)		
restriction of physical activity	71**	42**
problem with appearance	80	77

** p = 0.002

HUI3 overall utility score

proxy · self

mean score in ALL

1.00
0.80
0.60
0.40
0.20
0.00
-0.20

vision
ambulation
emotion
pain

NOT hearing
speech
cognition
dexterity

84

mean score in ALL

CSI + chemo   CSI   CSI + chemo   CSI

treatment arm
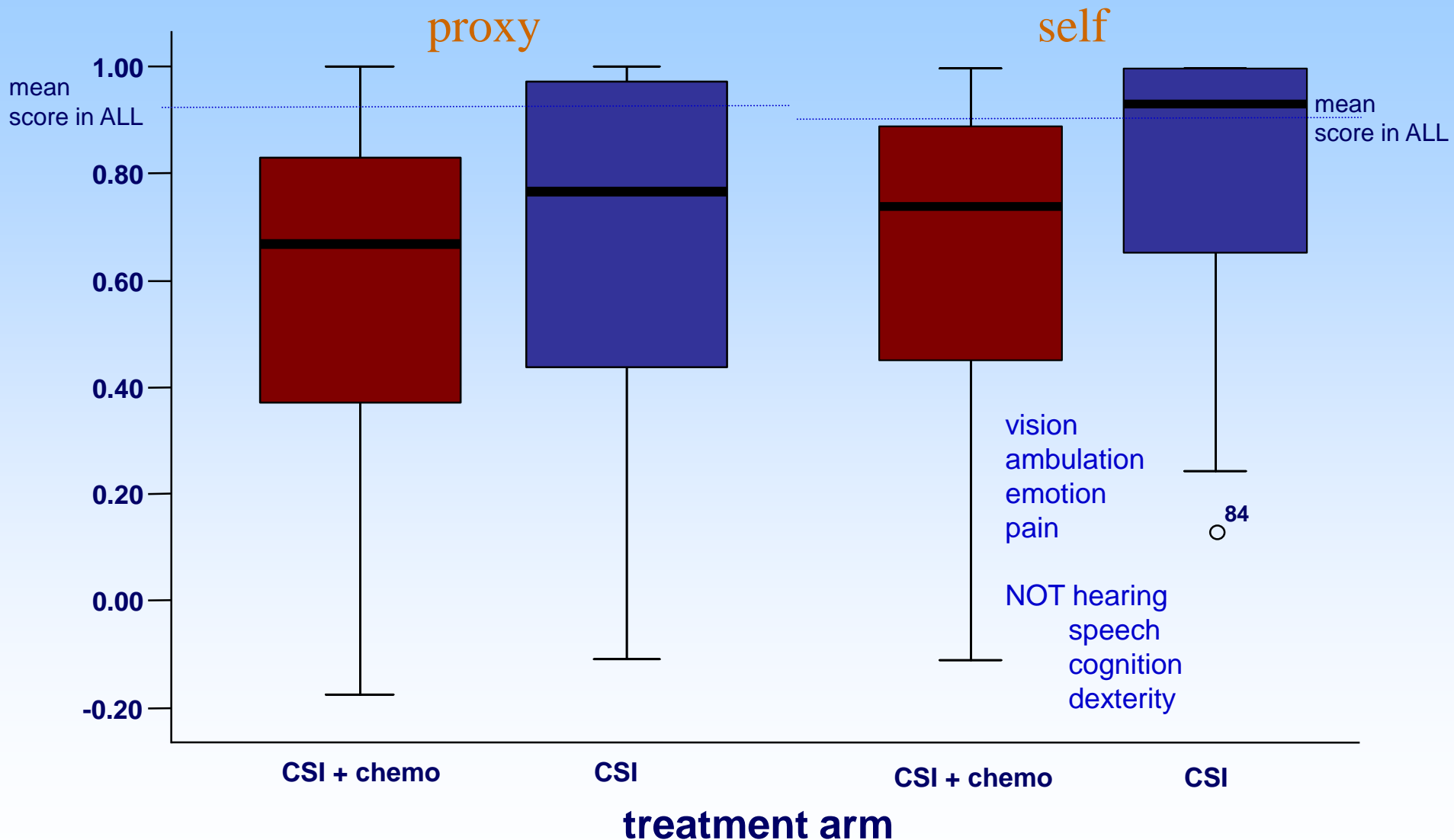
n = 114, p = 0.086, two-tailed;
p <0.05 for 12-17yrs (n = 63) and ≥18yrs (n = 32)

n = 98, p = 0.001, two-tailed

'Primary' QoS outcome scores in PNET3

Table 3. Comparison of Primary Outcomes Scores in All Patients (age 6-24 years)

Measure	CSI			CSI + CT			Mean Difference	95% CI†	P†
	No. of Patients	Median*	IQR*	No. of Patients	Median*	IQR*			
HUI									
Self report	48	0.93	0.65-1.00	38	0.71	0.48-0.89	−0.15	−0.27 to −0.03	.003
Proxy report	58	0.76	0.44-0.97	39	0.61	0.35-0.78	−0.09	−0.21 to 0.03	.075
SDQ total difficulties									
Self report	39	10	7.5-13.0	26	10.5	7.0-15.0	1.74	−1.05 to 4.54	.358
Proxy report	46	11	7.0-15.0	27	14.0	10.5-21.5	3.84	0.55 to 7.13	.023
PedsQL									
Self report	46	78.3	69.6-87.0	27	73.9	66.8-81.0	−3.5	−9.1 to 2.1	.18
Proxy report	46	74.0	64.6-88.5	27	67.7	57.8-79.7	−6.5	−13.2 to 0.2	.052
CHQ-PF28 proxy report									
Physical	46	48.6	37.2-55.0	25	32.0	16.7-52.0	−10.2	−18.6 to −1.9	.028
Psychosocial	46	52.1	43.8-56.6	25	45.1	34.9-54.5	−6.4	−12.8 to −0.02	.097
QLQ-C30 Global Health Status	14	83.3	75.0-100	14	83.3	75.0-91.7	−2.38	−14.9 to 10.2	.64
BN-20 motor dysfunction	14	100	66.7-100	14	66.7	44.4-88.9	−21.43	−41.6 to −1.2	.024

effect of addition of chemotherapy to CSI

The addition of chemotherapy to craniospinal irradiation appears to have a negative impact on various aspects of quality of survival which seems to continue into adulthood

- CSI + chemo children had lower overall health status (HUI)
- CSI + chemo children were significantly more restricted from participating in physical activities which seems to have an impact on social functioning (MES, HUI, CHQ, QLQ-C30, BN20).
- CSI + chemo children received significantly more help at school (MES, HUI)
- CSI + chemo children exhibit significantly more total difficulties with emotion and behaviour (SDQ)

Chemotherapy may sensitize the child to the unwanted effects of surgery and/or irradiation

Bull et al, *JCO* 2007, 25: 4239-4245

cerebellar tumours
as an example (contd)

2. Variations on radiotherapy

Sterotactic

Intensity modulated

Proton beam

Hyperfractionated

The HIT-PNET4 RCT

HFRT > effect on rapidly dividing cells 'early reacting' cells of the tumour and < effect on slower dividing normal CNS cells.

PNET4 experimental treatment arms designed to deliver higher biologically effective dose to tumour and be 'iso-toxic' for CNS

Standard radiotherapy (STRT) : RT x 1 per day + chemo

Vs

Hyperfractionated radiotherapy (HFRT): RT x 2 per day + chemo

BUT

- >5 yr EFS is 77$\pm$2 % with no difference between treatment arms.
- **If no difference in EFS… what about QoS?**

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PNET 4 cross-sectional outcome study

Aim

To identify differences in QoS between the two treatment arms in PNET4.

Participants

Event-free survivors in F, DE, I, NDL, ESP, SWE, & UK who had been enrolled in PNET4 between Jan 2003 & Nov 2006.

Methods

- Growth and medication use recorded prospectively .
- Self- and parent- report responses to questionnaire booklets administered between Aug 2010 and May 2011:
- Principal outcomes: executive function, health status, behavioural difficulties and quality of life

Demographic characteristics of participating survivors: 151 of 244 (62%) eligible survivors provided information

	HFRT n=74	Standard n=77
% Female	31	40
Mean age in years (range)	16 (7-30)	16 (9-30)
Mean age in years at diagnosis (range)	10 (3-21)	10 (3-20)
Mean time in years from diagnosis (range)	6 (4-10)	6 (4-10)

The two groups were also similar with respect to:
- post-surgical status and complications,
- baseline height and weight,
- birth weight and mid-parental target height
- peri-operative complications

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Executive Function (BRIEF) in all participants
by parent report if <18 yrs or self report if $\geq$ 18 yrs
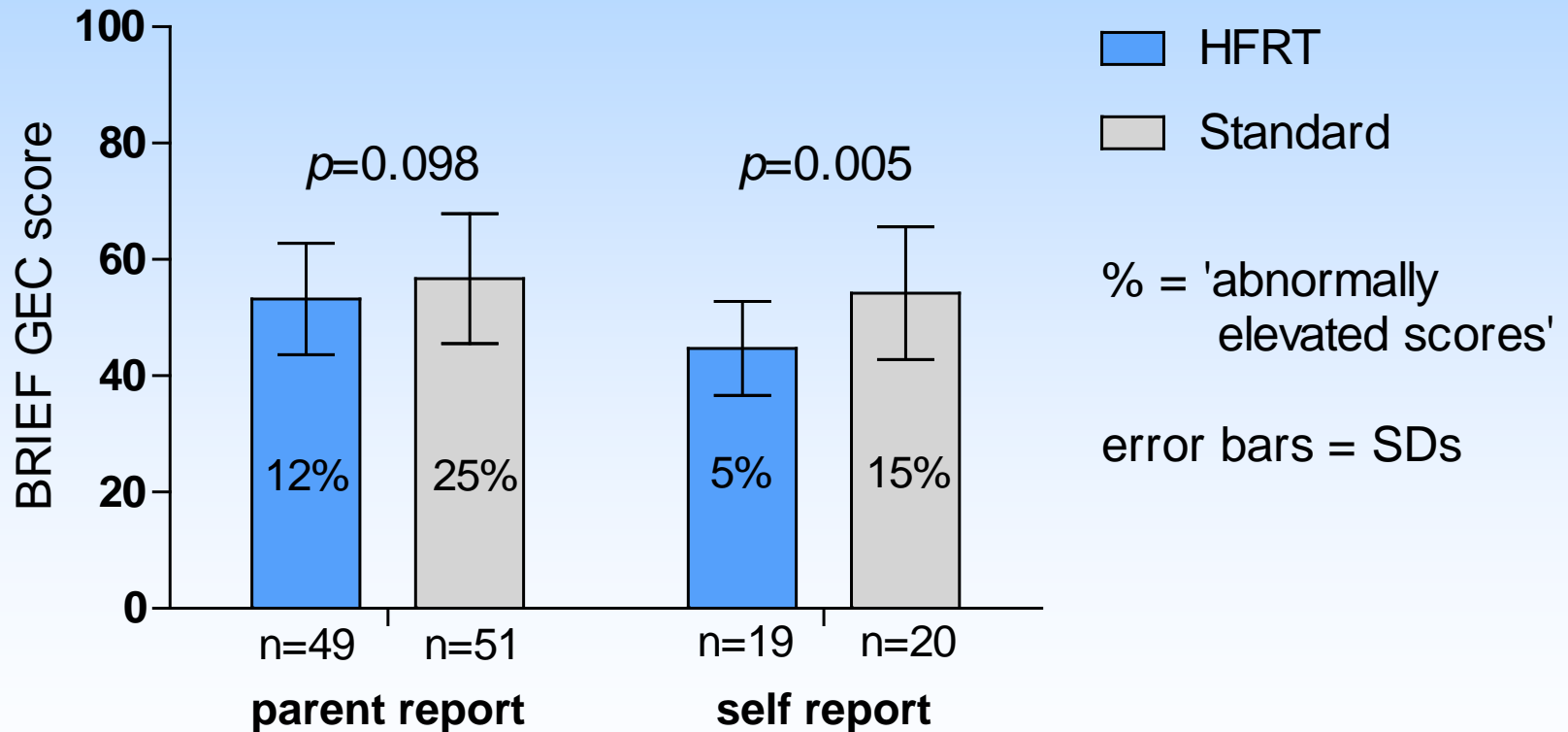
Overall % of 'abnormally elevated scores: HFRT Vs STRT = 7/68 (10%) Vs 16/71 (23%)

Multiple regression model

Executive functioning (combined z-scores, N=130)

1. Effect of treatment arm after adjusting for sex, age at diagnosis, time since diagnosis, post-op complications.

Group mean Z scores		Mean difference (95% CI)	P	Adjusted mean difference (95% CI)	P
HFRT n = 68	STRT n = 71				
-0.25	0.24	**0.48** (0.2, 0.8)	**0.004**	**0.42** (0.1, 0.8)	**0.017**

Growth (UK norm z-scores)

Mean (95% CI) height and height deficit from baseline
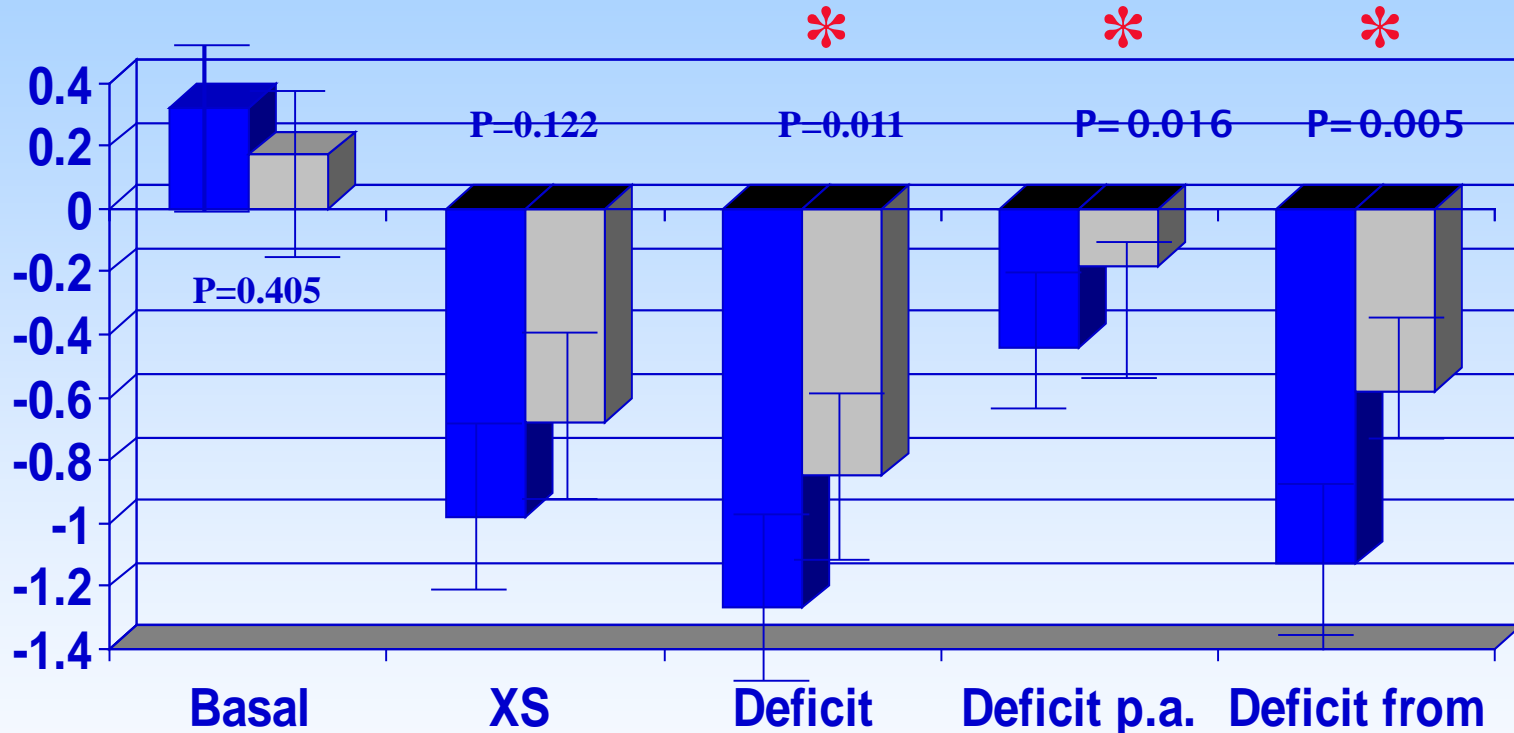
- All survivors short and thin vs UK norms
- No difference in weight/BMI between arms

PNET 4 cross-sectional outcome study:
Principal QoS outcomes by treatment, stratified by age

| Mean z-scores (SDs) | n1, n2 | <8.0 years at diagnosis | | | | n1, n2 | >8.0 years at diagnosis | | | |
		HFRT	STRT	Inter-group mean difference (95% CI)	P		HFRT	STRT	Inter-group mean difference (95% CI)	P
Executive function (BRIEF)	29, 24	-0.45 (0.83)	0.39 (1.11)	-0.84 (0.31 to 1.38)	0.003	39, 47	-0.09 (0.88)	0.16 (1.03)	-0.25 (-0.17 to 0.67)	0.24
Health status (HUI3)	26, 21	0.14 (0.76)	-0.09 (1.13)	0.23 (-0.32 to 0.79)	0.41	29, 38	0.10 (0.94)	-0.17 (1.22)	0.27 (-0.28 to 0.82)	0.33
Behavioural difficulties (SDQ)	31, 23	-0.18 (0.75)	0.30 (1.17)	-0.48 (-0.09 to 1.04)	0.10	19, 27	-0.02 (1.09)	-0.05 (1.03)	0.03 (-0.61 to 0.67)	0.93
Quality of Life (PedsQL & QLQ-C30)	20, 17	0.18 (1.04)	-0.06 (1.01)	0.23 (-0.45 to 0.92)	0.50	42, 49	0.02 (1.01)	-0.07 (0.98)	0.10 (-0.32 to 0.51)	0.64
Height decrement from diagnosis	23, 17	-1.62 (0.85)	-0.91 (0.84)	-0.71 (-1.26 to -0.17)	0.012	36, 39	-1.05 (0.88)	-0.82 (0.89)	-0.23 (-0.64 to 0.18)	0.26
Weight decrement from diagnosis	24, 19	-0.23 (1.13)	0.02 (1.04)	-0.25 (-0.92 to 0.43)	0.47	35, 41	-0.53 (0.93)	-0.31 (0.84)	-0.21 (-0.62 to 0.19)	0.30

Psychometric assessments in HIT-PNET4 RCT

- Separate national efforts to assess in France, Germany, Italy, Sweden combined into single dataset of z-scores

- Mean FSIQ for the whole group around 1SD below norms: consistent with the literature

- No significant difference between treatment arms for the whole group

- However results suggest an advantage of HFRT for subsequent cognitive functioning in those aged <8y at diagnosis, significant for Verbal IQ

- Consistent with better executive functioning reported by Kennedy (2014) in same age range

cerebellar tumours
as an example (contd)

3. Factors other than adjuvant anti-tumour treatment

'In depth' study

Patients

- Children aged 8 to 14 years diagnosed within last three years at 11 CCLG centres in UK

- Comparison group recruited from same schools and year groups as brain tumour participants

Methods

- Child and parent questionnaires:,
  - Health Utilities Index
  - Behavior rating inventory of executive function (BRIEF)
  - Strengths and Difficulties Questionnaire (SDQ),
  - Attributional Style Questionnaire (ASQ),
  - General Health Questionnaire (GHQ-12),
  - Pediatric Quality of Life Inventory (PedsQL).
- Psychometric assessment of child: WISC-IV
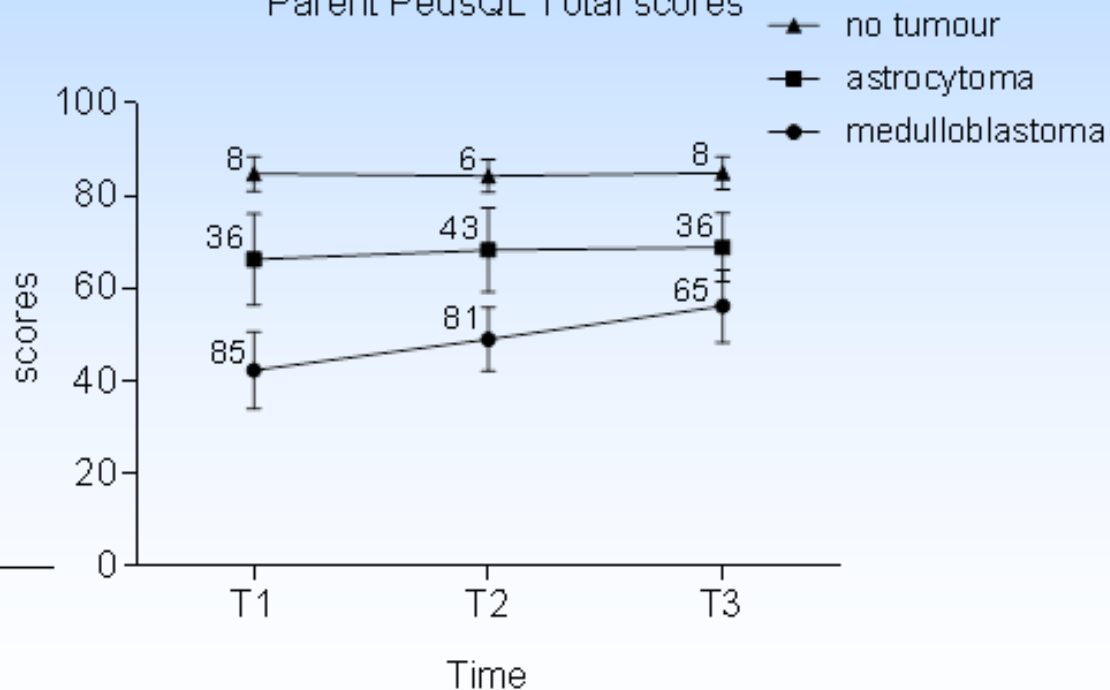
In-depth study WISC-IV scores by group
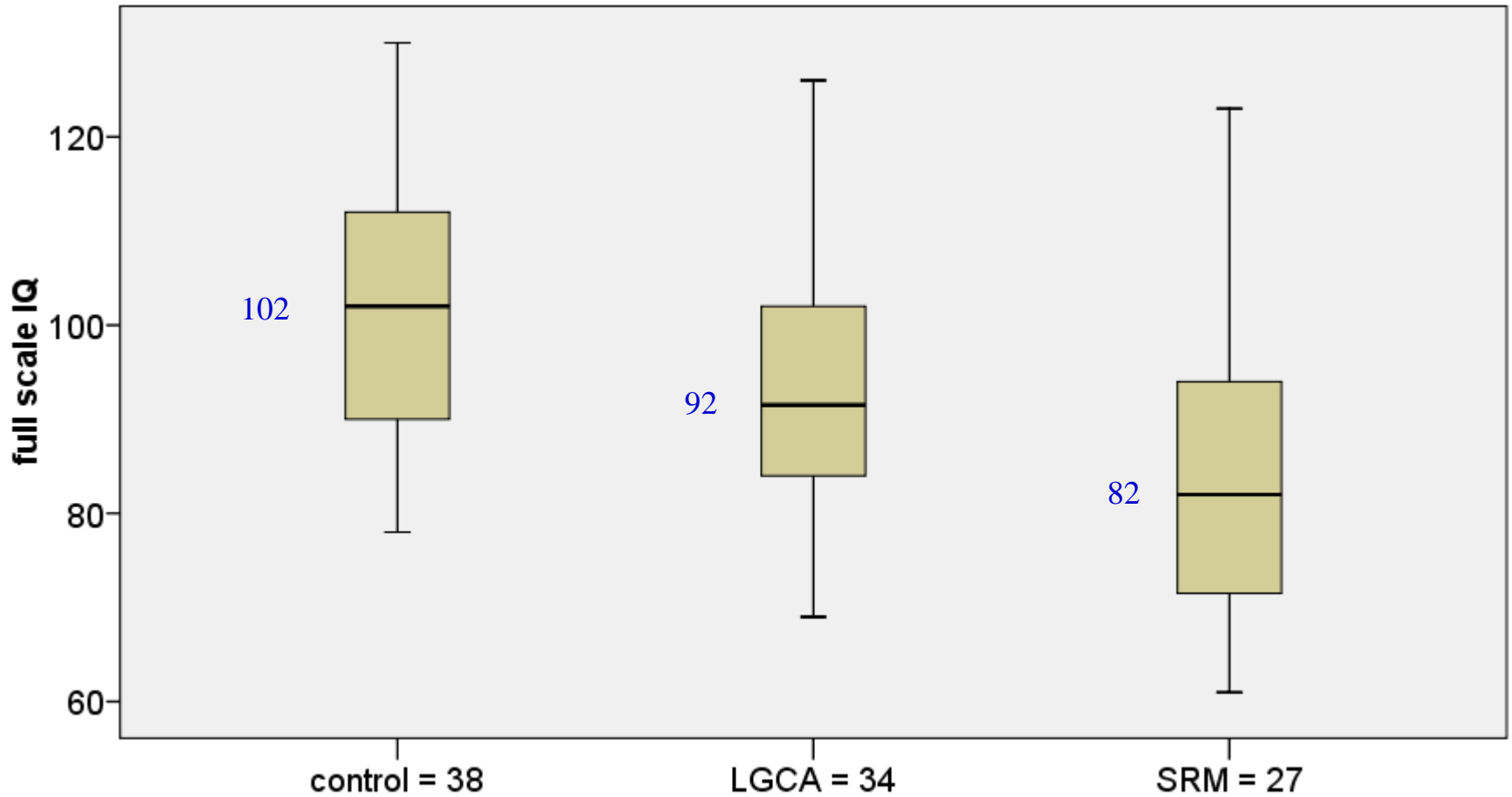
'In depth' study: Quality of Life scores over 24 month follow-up period in 90 old children aged 8-14 years. ('Complete cases' only.)
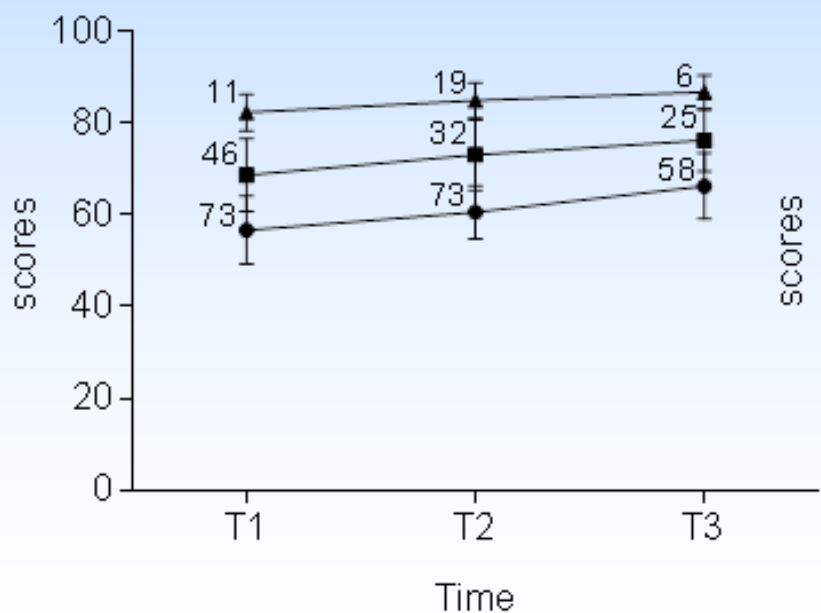
'In depth' study of 8-14 year old children with cerebellar tumours

Table 4. Factors at study entry predicting quality of life: child-report 24 months later

	B	95% CI for B	P
Final model $n=81$, $R^2=0.534$, $R^2_{adj}=0.516$, $P<.001$			
Child's age (years)	−0.136	−0.263 to −0.009	.036
Emotion z score	−0.100	−0.178 to −0.022	.013
Cognition z score	−0.037	−0.053 to −0.020	<.001

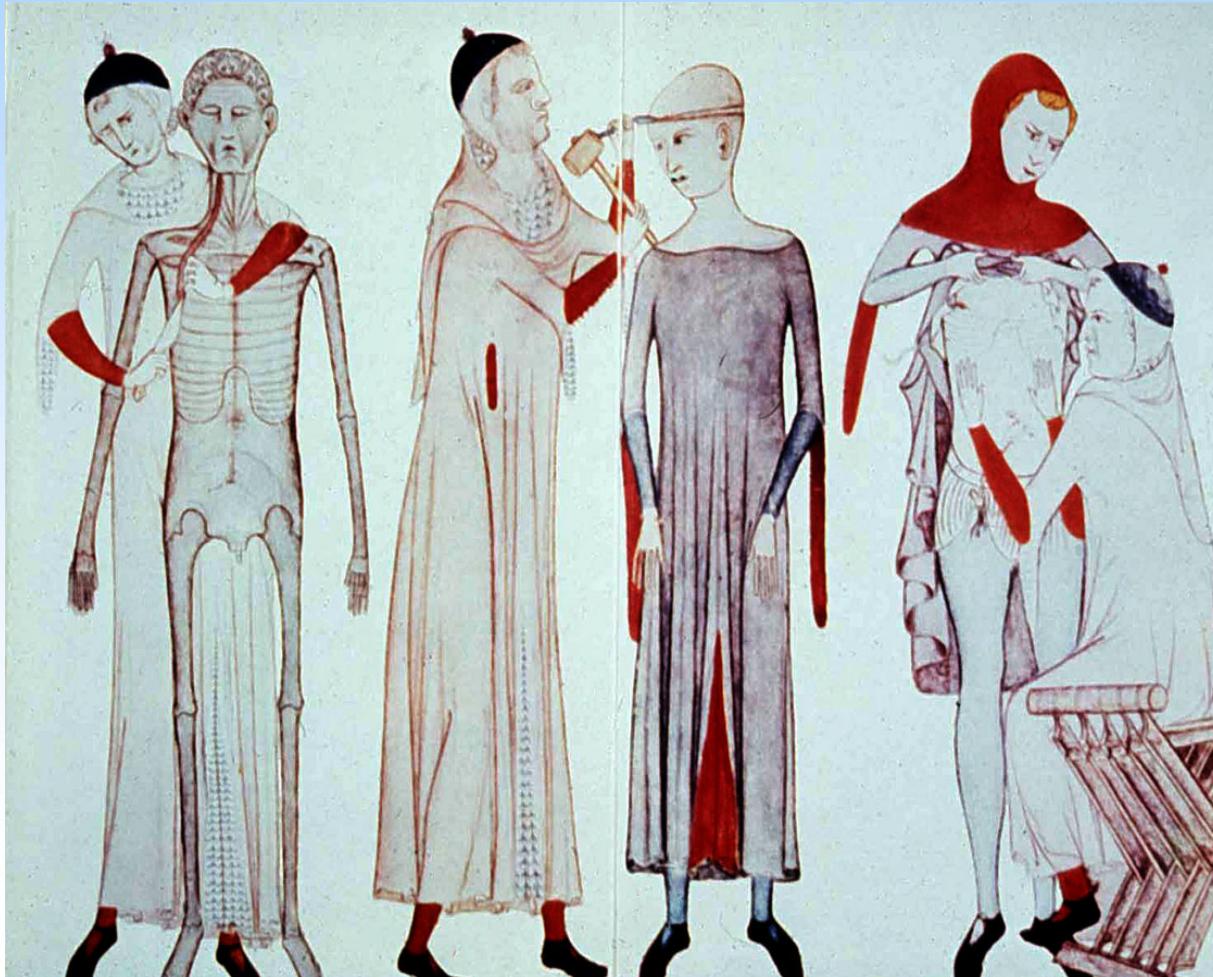**Table 5.** Factors at study entry predicting quality of life: parent-report 24 months later

	B	95% CI for B	P
Final model $N=81$, $R^2=0.644$, $R^2_{adj}=0.631$, $P<.001$			
Emotion z score	−0.111	−0.196 to −0.026	.011
Motor and sensory z score	−0.019	−0.032 to −0.006	.004
Cognition z score	−0.043	−0.063 to −0.023	<.001

Conclusion

Early screening of cognitive and emotional function in this age group would identify those at risk of poor HRQoL.

4. neurosurgery: the forgotten factor?

the cerebellar cognitive affective syndrome

- disturbance of executive function including poor planning

- visual-spatial disorganization and impaired visual-spatial memory

- personality change with blunting of affect or disinhibited and inappropriate behaviour

- difficulty with interpreting and producing logical sequences

- language difficulties including dysprosodia, mild anomia, and agrammatism

The Cerebellum and Cognition

EDITED BY

JEREMY D. SCHMAHMANN

Clinical neurologic features before and after tumour resection

	Medulloblastoma n=37		Cerebellar astrocytoma n=35	
	Pre resection n (%)	Post resection n (%)	Pre resection n (%)	Post resection n (%)
Severe hydrocephalus	17 (46)	4 (11)	12 (34)	4 (11)
Visual impairment	7 (19)	9 (24)	6 (17)	4 (11)
Speech impairment	3 (8)	11 (30)	1 (3)	6 (17)
Upper limb ataxia	19 (51)	19 (51)	12 (34)	9 (26)
Truncal ataxia	23 (62)	24 (65)	7 (20)	8 (23)
Limb weakness	1 (3)	12 (32)	2 (6)	5 (14)
Balance impairment	24 (65)	27 (73)	17 (49)	9 (26)
Walking impairment	15 (41)	18 (49)	11 (31)	10 (29)
Seizures	0	0	2 (6)	0
Cerebellar mutism	0	12 (32)	0	4 (11)
CNS/other infection	0	8 (22)	0	5 (14)
No adverse features	5 (14)	4 (11)	7 (20)	12 (34)
Mean no. of clinical features (SD)	4.1 (2.8)	5.7 (4.1)	2.7 (2.2)	2.9 (3.2)

Pervasive themes in medium and long term quality of survival after childhood brain tumours

- morbidity is high
    - -- cognition
    - – health state (multi-dimensional)
    - – education, employment
    - – behaviour
    - – quality of life

- irradiation can reduce QoS but irradiation alone does not account for most problems and radiobiology is not clear.

- also tumour, surgery, chemotherapy, psychosocial factors.

- On-line tools beginning to play a role in assessing QoS: this is a promising method of using patient reported outcomes and may be useful for care of individual patient

END