

# Developmental Strategies for Children with Cancer

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Developmental-Behavioral Pediatrics



# Development of Children with Cancer

- The Numbers
- The Outcomes
- The Interventions (real and proposed)
- Areas for Future Study

# The Numbers

## Childhood Age-Adjusted Invasive Cancer Incidence Rates and 95% Confidence Intervals by Primary Site and Age, United States (Table 1.2.5.1)

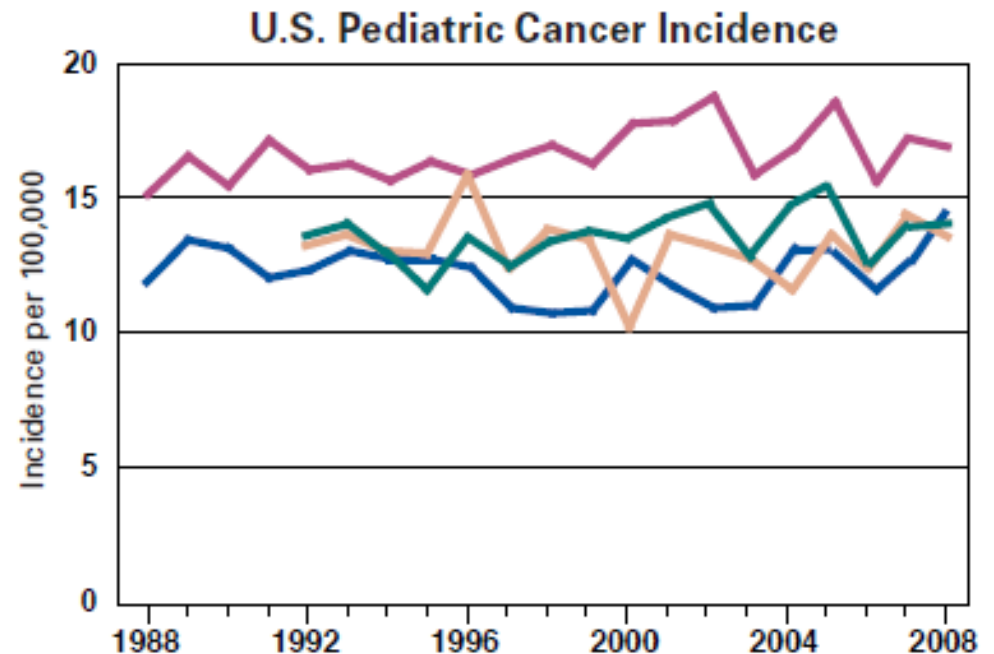
Rates are per 100,000 persons and are age-adjusted to the 2000 U.S. standard population (19 age groups - Census P25-1130).

Cancer Types	Age	
	0-14	0-19
All Cancer Sites Combined	15.5	17.0
Bones and Joints	0.7	0.9
Brain and Other Nervous System	3.3	3.0
Hodgkin Lymphoma	0.6	1.3
Kidney and Renal Pelvis	0.9	0.7
Leukemia	4.8	4.4
Acute Lymphocytic	3.8	3.3
Acute Myeloid	0.7	0.7
Non-Hodgkin Lymphoma	0.9	1.1
Soft Tissue	1.0	1.0
Other	3.2	4.6

# The Numbers

## (Incidence Rising)

- The incidence of children diagnosed with invasive cancer has risen from 11.5 cases per 100,000 in 1975 to 15.5 per 100,000 in 2008.
- The incidence of childhood leukemias was 3.3 cases per 100,000 in 1975 and 4.8 cases per 100,000 in 2008.
- For childhood brain tumors, the overall incidence rose from 1975 through 2008, from 2.3 to 3.3 cases per 100,000, with the greatest increase occurring from 1983 through 1986 (however, there is some thought that this represents a false increase attributable to new imaging techniques and less stringent diagnostic criteria).



# The Numbers

(Death Rates Declining)

- Over the past 20 years, death rates from cancer in children have decreased.
- Five-year survival rates for all childhood cancers combined have increased from 58.1 percent in 1975-1977 to 79.6% in 1996-2003.

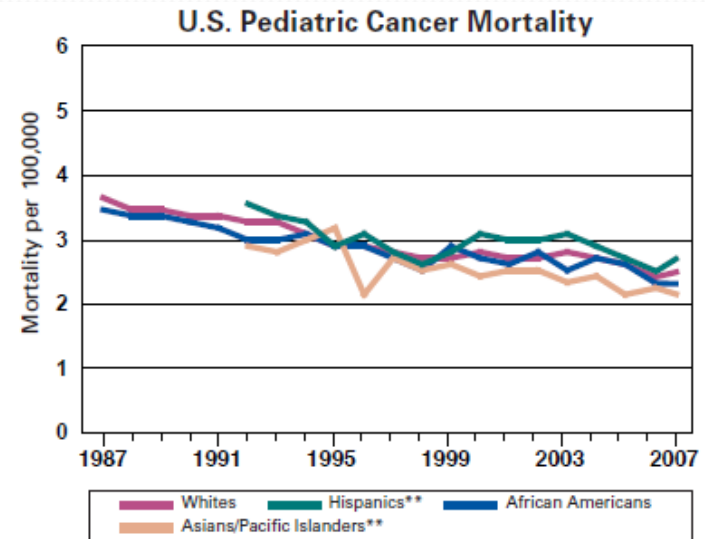
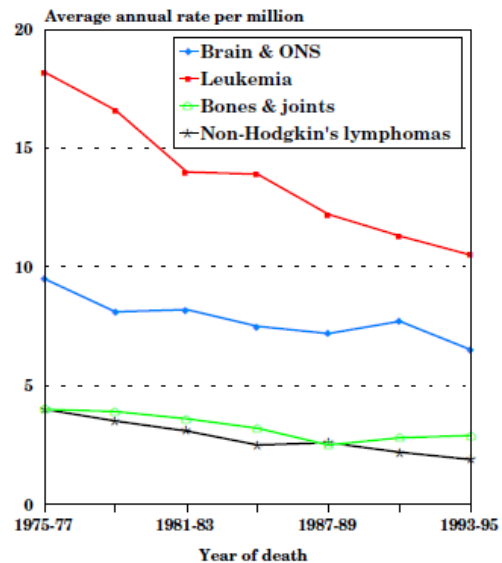


Figure XIV.8: Trends in age-specific cancer mortality rates by type, age 10-14, all races both sexes, United States, 1975-95





# The Numbers

(So how many young survivors are there?)

- National Cancer Institute estimates suggest there are 600,000 survivors of cancer below the age of 40 living in the U.S.
- Twenty percent of that population (120,000) are below the age of 20.
- This represents a near four-fold increase in the number of young cancer survivors as compared to the 1970's.



# The Outcomes

- Although falling mortality rates from childhood cancer are the result of laudable medical advances, this population presents a challenge to pediatricians.
- Specifically, expectations for the development of survivors of CNS malignancies remain hard to predict.
- As such, appropriate developmental strategies need further development and evaluation.



# The Outcomes

- In the early era of cancer survivorship, there was a belief that treatment did not correlate with long-term neurocognitive effects.
- In 1981, Meadows et al published study suggesting that treatment of leukemia with cranial irradiation led to significant declines in IQ
  - 18 patients tested pre- and post-treatment with variety of batteries (Stanford-Binet, Wechsler, etc.)
  - Group receiving cranial irradiation (prophylactic dosing) had steep declines in IQ scores





# The Outcomes

- Fletcher and Copeland [1988] indicated that whole brain treatments for childhood malignancies appeared to differentially impact the nondominant hemisphere. Reported most common deficits: visual-motor integration, attention abilities, and processing speed.
- Mulhern and Butler [2006] further validated these initial impressions; clarified that whole brain radiation and intrathecal chemotherapy tend to lead to deficits in spatial awareness and impaired attention/concentration, particularly under conditions of vigilance.
- The resultant manifest deficit in survivors is commonly apparent in the area of arithmetic/mathematics.
- Language less affected unless patient particularly young, treatment particularly aggressive, or patient female.



## The Outcomes (cont'd)

- Compared with siblings, rates of neurocognitive impairment (a score below the 10th percentile of the sibling group's scores) were higher in all CNS survivor diagnostic groups after treatment with radiation.
- Greater than 40% of medulloblastoma or primitive neuroectodermal tumor survivors had impaired attention and/or processing speed function.
- Dose-response relationship with RT appreciated with astrocytomas (31->53%) and glial tumors (not medulloblastomas or neuroectodermal tumors)

# The Outcomes (the clincher)

- Many childhood brain tumor survivors experience deficits in social competence at the level of social adjustment. These deficits worsen with time.
- Age and sex-matched siblings more likely than survivors to report employment (RR 1.4, 95% CI 1.3-1.5), an income greater than \$20,000 (RR 1.2, 95% CI 1.1-1.3), marriage (RR 2.0, 95% CI 1.8-2.2), and college graduation (RR 1.4, 95% CI 1.3-1.5).
- CNS tumor survivors frequently require use of special education services during childhood, with increasing use based on younger age at diagnosis: age at diagnosis 0-5 years, 70% of survivors access special educational services; 6-10 years, 58%; 11-15 years, 32%; 16-20 years, 24%.
- CNS tumor survivors differ from those with other primary cancers in having more adverse outcomes in terms of education, employment, and health status and quality of life.

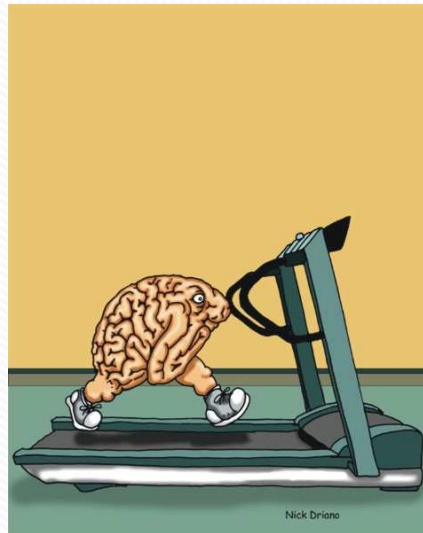
# Interventions

How can we help survivors of childhood cancer?

Nicole Glenn MD

# Overview

- Pharmacologic Interventions
- Cognitive Behavioral Rehab: CRT
  - School based intervention
  - COG recommendations



# Pharmacologic Interventions

- Because most common neurocognitive deficit seen was in vigilance, attention, and processing speed-there have been multiple trials of the use of methylphenidate (Ritalin) to improve these measures in children treated for ALL and brain tumors with cranial radiation or intrathecal chemotherapy
- ALL and malignant brain tumor survivors have increased incidence of neurocognitive impairments such as declining IQ and academic achievement. This may possibly be related to deficits in attention and working memory from a less than normal volume of white matter development.
- Early studies:
  - DeLong et al. [1992] published one of the first efforts to pharmacologically treat neurocognitive functioning in pediatric survivors of a CNS-related malignancy. Approximately 75% of the participants who received methylphenidate exhibited a “good response”.
  - Meyers et al., [1998] suggested that methylphenidate was effective in improving neurocognitive functioning (information processing speed, memory, mental flexibility, mood, ADLs, and affect) within the adult brain tumor population



## RCT's of Ritalin-Thompson 2001

- 104 (32 enrolled) subjects who were treated for ALL or brain tumor, aged 6 to 18, have been cancer free for 24 mo, and have English as primary language.
- Excluded if had ADHD dx before developing cancer, h/o tics, glaucoma, use of psych meds, uncontrolled seizures, or h/o substance abuse.
- Day 1, subjects had neurocognitive measurements at baseline, including Weschler IQ, CBCL, Connors Continuous Performance Test, Weschler Indiv. Achievement Test, California Verbal Learning Test, and Visual Auditory Learning Test. Excluded if scored significant on measure of anxiety or depression
- Included if IQ >50, with attention measure/CPT <16th%tile (1 DS below normal for age and gender), and at least 1 area of academic measure 1 SD below on WAIT.
- Group as a whole had IQ average 84.9, reading 87, spelling 85, math 85, and error rate 8.8% on CPT
- Placebo controlled, DB RCT. Day 2, retested with CPT, CVLT, and VAL 90 minutes after placebo or 0.6mg/kg Ritalin.
- Found significantly improved functioning associated with methylphenidate in terms of both sustained attention, fewer errors of omission and overall CPT score. Impulsive responding, processing speed, and reaction time did not differentiate the groups. In addition, no significant change was seen in CVLT and VAL testing.
- Flaws/limitations: Small sample size, study was discontinued prior to expected enrollment, highly significant "practice effects" as participants take the test twice, short term outcome

## RCT's of Ritalin- Mulhern 2004

- 83 subjects, treated for ALL or brain tumors at least 12 months prior, age 6-18 years old with English as primary language
- Excluded: prior ADHD dx, seizures, tics, glaucoma, endocrinopathies, blindness, deafness, drug abuse, psych med use, recurrent disease, drug adverse reaction. Also- could not reside within 60 miles of treatment center as to not compete with another study
- Initial screening: IQ>50 (Wechsler estimation), CPT with error of omission >75%tile, WAIT (academic achievement) score <90 in at least one area, and Connors Rating Scales (parent and teacher) >75 on one or more ADHD index. Any CBCL with >65 on anxiety/depression had diagnostic interview to r/o mood disorder and if present, excluded.
- Observed blinded after taking Ritalin 0.6 mg/kg or placebo for medication reactions
- Randomized, double blinded Home cross-over trial for 3 weeks to 1 of 6 medication regimens: low dose placebo moderate dose, mod low placebo, mod placebo low, placebo low mod, placebo mod low, (Low 0.3mg/kg max 10, mod 0.6mg/kg max 20)
- Received doses M-F with washout on weekends
- CRS by parents and teachers taken weekly via telephone as well as SERS, Social Skills Rating
- 83 at least 1 week, 74 all weeks, all at single site
- CRP from parents and teachers showed significant improvement on both low and moderate dose regarding inattention, problems with cognition, and symptoms of ADHD. Teachers saw improvement in hyperactivity. Differences measured as >3 point raw improvement in scores. Significant improvement in social competence and academic competence with low and moderate dose, greater with moderate. Improvement in problem behaviors were seen at moderate dose only by teachers.
- No differences were seen between moderate and low dose. More side effects and less tolerance seen in brain tumor patients
- Limitations-Can this be extrapolated to extended time periods? Phone reports accurate? Outcome is affected by sequence and timing of the cross over and carry over effect from week to week. What does this imply for long term neurocognitive outcomes?



# Psychologically based brain rehab efforts

- Research led by Dr. Butler PhD at Oregon Health & Sciences University has been leading research in [Cognitive Remediation Therapy](#). Started in 1998 case study of a brain tumor survivor with attention deficits-

Included:

- “Traditional massed practice rehab” (drill exercises to improve neurocognitive functioning and CNS efficiency)
- Meta- cognitive strategies (attend to thinking and process response to attentional memory and information process demands)
- Cognitive behavioral psychotherapy (CBT) to resist distraction (CBT- attend to self thoughts and apply behavioral principles of reinforcement and modeling with therapist)
- Focuses on attentional skills and learning strategies. CRT teaches specific strategies to improve performance on cognitive and school-related activities.
- Individual therapist observes the patient in a cognitive process. “Ineffective strategies were identified, and new approaches were taught. For example, children learn basic strategies, such as how to psychologically prepare for success, systemically and completely scan stimulus material, periodically check their own performance, refrain from engaging in self distracting behaviors, set personal goals, and attempt new problem-solving strategies”
- Activities promote arithmetic concept development, particularly fractions and other visual-spatial aspects of mathematics. This was included because of the common finding of an arithmetic learning disability in children who received irradiation and other CNS treatments.
- To increase generalization, children bring their school homework into therapy

## Does CRT work?

- In 2008, Butler performed RCT of CRT outcomes
- 161 patients age 6-17 years old randomly assigned to CRT or control "wait list".

Initial testing included:

- Academic Achievement

Wide Range Achievement Test, Calculation and Applied Problems, Reading Comprehension with Peabody Individual Achievement Test, Arithmetic with WICS

- Brief Focused Attention

Digit span WISC III, Sentence Memory, Stories with Children's Memory Scale, Rey Auditory Verbal Learning Test

- Working Memory

WISCIII Digit span back, Stroop Color Word Test, Trail Making Test, Brief Test of Attention

- Memory Recall

Stories Delayed Recall, Rey Osterrieth Complex Figure Test

- Vigilance


CPT

- Metacognitive learning strategies, self-esteem in regards to academic

- 20 two-hour sessions in intervention group
- Individuals who completed the CRT demonstrated significantly improved academic achievement in language and mathematics. Parents significant improvement in attention/concentration.
- No statistically significant improvements in neurocognitive functioning were seen in the intervention group, as both groups made improvements over time. Possible practice effect??

## School based intervention

- Both hospital and intervention when returning to traditional school settings
- Regardless of type of cancer (CNS vs. non CNS), children are at risk 2/2 missed school days, interrupted study, isolation with home programs, fatigue, immunosuppressant medications, and many other factors.
- Counselor-liaison professionals: provide educational planning, advocacy, and coordination of school reentry services. Guide options for continued academic development during treatment, facilitate communication between the hospital staff and community educational professionals, and support the development of appropriate educational planning during transitions in academic placement, such as reentry into community school settings
- -Study by Mitby [2003] of 12430 survivors and 3410 sibling controls showed that special education services were accessed by 23% of survivors and 8% of siblings. The greatest differences were seen in those diagnosed before age 6 years, and those with CNS tumors.
- Most long-term survivors of childhood cancer completed high school, but survivors of leukemia, CNS tumors, non-Hodgkin lymphoma, and neuroblastoma were significantly less likely to finish high school and college when compared with siblings.



## Guidelines for Identification of, Advocacy for, and Interventions in Neurocognitive Problems in Survivors of Childhood Cancer 2007

1. All childhood cancer survivors at risk for neurocognitive difficulties should have a baseline evaluation at the time of entry into long-term follow-up, even in the absence of any overt manifestation of CNS injury
2. Survivors who experience school difficulties for the first time should be referred for a neuropsychological evaluation, regardless of their previous cancer or treatment.
3. Although children with brain tumors and ALL are at greatest risk, children with other cancers who experience prolonged school absences should undergo evaluation before school reentry.
4. Recommendations for repeat testing after baseline evaluation should consider the anticipated trajectory of the emergence of late effects and the child's specific medical and developmental risk factors. Reevaluation is often recommended when children transition to new schools or if new difficulties emerge.
5. The developmental status of survivors, including their education and vocational progress and their general adaptive functioning, should be assessed annually by their primary health care provider.
6. Regarding IEP's recommend advocating for a more complete evaluation beyond an IEP, with a neuropsychologist familiar with this population and late effects

## Role of the primary pediatrician: COG recommendations

- (1) being attentive to the potential for neurocognitive late effects
- (2) helping parents identify professionals in the community who can conduct appropriate evaluations
- (3) providing information about patient rights
- (4) providing written summaries about the child's health/cancer history that can be used as supporting documentation for school placement and accommodations

<http://www-survivorshipguidelines.org/pdf/EducationalIssues.pdf>



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