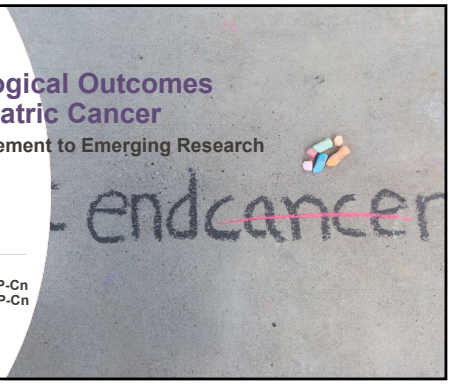
Neuropsychological Outcomes Following Pediatric Cancer

From Clinical Management to Emerging Research



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June 23, 2022

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No Conflicts of Interest

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Learning Objectives

At the completion of this workshop, attendees will be able to:

- **Describe** Disease and treatment-related risk and mitigating factors associated with cognitive outcomes from CNS and non-CNS cancers in children
- **Describe** Socioeconomic and sociocultural factors that affect cognitive and functional outcomes following pediatric cancer
- **Identify** Educational implications and best practices for optimizing educational support for pediatric cancer survivors, as well as emerging paradigms to improve cognitive outcomes following pediatric cancer

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Overview

Epidemiology of Pediatric Cancer

Neuropsychological Outcomes

Non-CNS and CNS cancers
- Disease Factors
- Treatment Factors
- Psychosocial Factors

Educational Outcomes

Non-CNS and CNS cancers

Clinical Management & Future Directions

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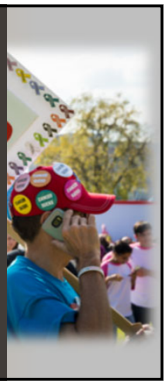
Epidemiology of Pediatric Cancer



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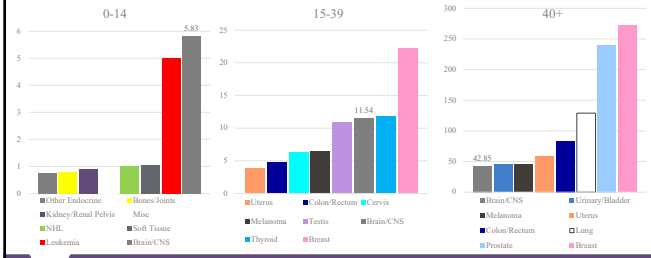
Average Annual Age-Adjusted Incidence per 100,000 (2012-2017)



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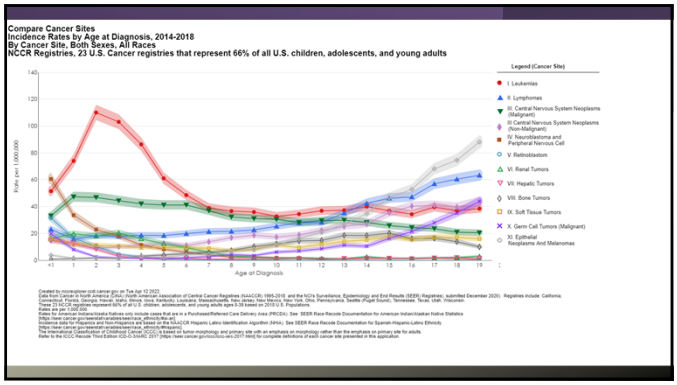
Compare Cancer Sites
Incidence Rates by Age at Diagnosis, 2014-2018
By Cancer Site, Both Sexes, All Races
NCCR Registries, 23 U.S. Cancer registries that represent 66% of all U.S. children, adolescents, and young adults
Legend (Cancer Site)
I. Leukemias
II. Lymphomas
III. Central Nervous System Neoplasms (Malignant)
III Central Nervous System Neoplasms (Non-Malignant)
IV. Neuroblastoma and Peripheral Nervous Cell
V. Retinoblastom
VI. Renal Tumors
VII. Hepatic Tumors
VIII. Bone Tumors
IX. Soft Tissue Tumors
X. Germ Cell Tumors (Malignant)
XI. Epithelial Neoplasms And Melanomas
Age at Diagnosis

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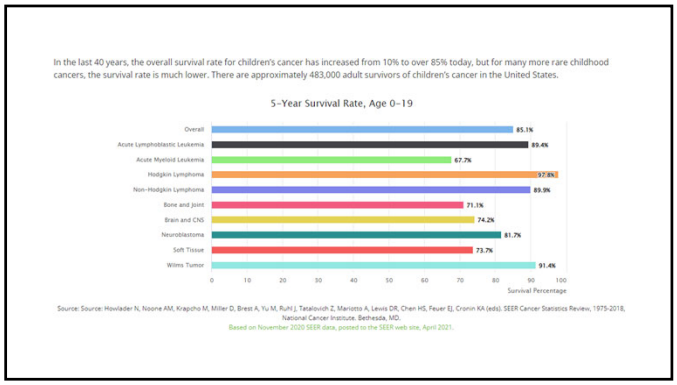
In the last 40 years, the overall survival rate for children's cancer has increased from 10% to over 85% today, but for many more rare childhood cancers, the survival rate is much lower. There are approximately 483,000 adult survivors of children's cancer in the United States.
5-Year Survival Rate, Age 0–19
Overall 85.1%
Acute Lymphoblastic Leukemia 89.4%
Acute Myeloid Leukemia 67.7%
Hodgkin Lymphoma 97.6%
Non-Hodgkin Lymphoma 89.9%
Bone and Joint 71.1%
Brain and CNS 74.2%
Neuroblastoma 81.7%
Soft Tissue 73.7%
Wilms Tumor 91.4%
Survival Percentage
Source: Source: Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD,
Based on November 2020 SEER data, posted to the SEER web site, April 2021.

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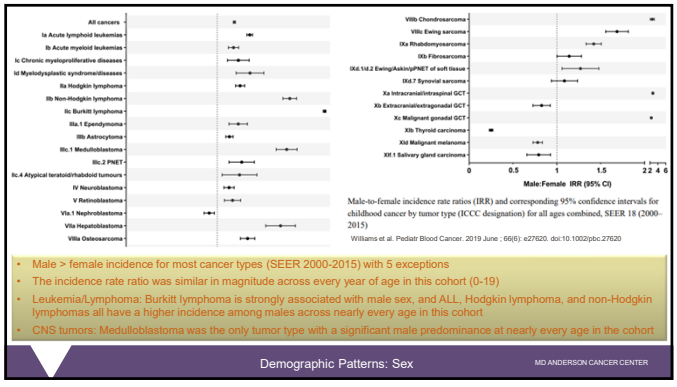
All cancers
Ia Acute lymphoid leukemias
Ib Acute myeloid leukemias
Ic Chronic myeloproliferative diseases
Id Myelodysplastic syndrome/diseases
IIa Hodgkin lymphoma
IIb Non-Hodgkin lymphoma
IIc Burkitt lymphoma
IIIa.1 Ependymoma
IIIb Astrocytoma
IIIc.1 Medulloblastoma
IIIc.2 PNET
IIc.4 Atypical teratoid/rhabdoid tumours
IV Neuroblastoma
V Retinoblastoma
VIa.1 Nephroblastoma
VIIa Hepatoblastoma
VIIIa Osteosarcoma
VIIIb Chondrosarcoma
VIIc Ewing sarcoma
IXa Rhabdomyosarcoma
IXb Fibrosarcoma
IX6.1id.2 Ewing/Askin/pPNET of soft tissue
IXd.7 Synovial sarcoma
Xa Intracranial/intraspinal GCT
Xb Extracranial/extragonadal GCT
Xc Malignant gonadal GCT
XIb Thyroid carcinoma
XId Malignant melanoma
XIf.1 Salivary gland carcinoma
0 0.5 1 1.5 2 2 4 6
Male:Female IRR (95% CI)
Male-to-female incidence rate ratios (IRR) and corresponding 95% confidence intervals for childhood cancer by tumor type (ICCC designation) for all ages combined, SEER 18 (2000–2015)
Williams et al. Pediatr Blood Cancer. 2019 June ; 66(6): e27620. doi:10.1002/pbc.27620
• Male > female incidence for most cancer types (SEER 2000-2015) with 5 exceptions
• The incidence rate ratio was similar in magnitude across every year of age in this cohort (0-19)
• Leukemia/Lymphoma: Burkitt lymphoma is strongly associated with male sex, and ALL, Hodgkin lymphoma, and non-Hodgkin lymphomas all have a higher incidence among males across nearly every age in this cohort
• CNS tumors: Medulloblastoma was the only tumor type with a significant male predominance at nearly every age in the cohort
Demographic Patterns: Sex
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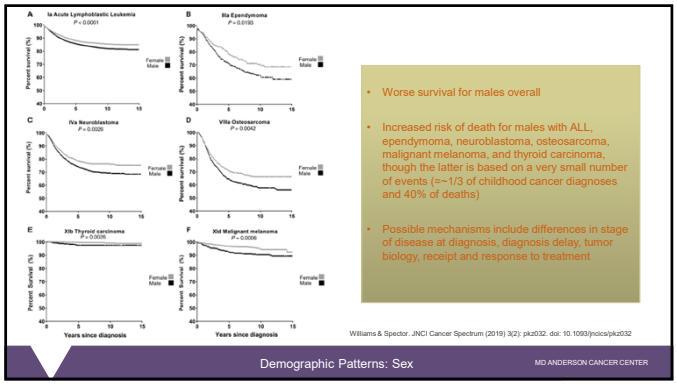

- Worse survival for males overall
- Increased risk of death for males with ALL, ependymoma, neuroblastoma, osteosarcoma, malignant melanoma, and thyroid carcinoma, though the latter is based on a very small number of events (~1/3 of childhood cancer diagnoses and 40% of deaths)
- Possible mechanisms include differences in stage of disease at diagnosis, diagnosis delay, tumor biology, receipt and response to treatment

Williams & Spector. JNCI Cancer Spectrum (2019) 3(2): pkz032. doi: 10.1093/jncics/pkz032

Demographic Patterns: Sex

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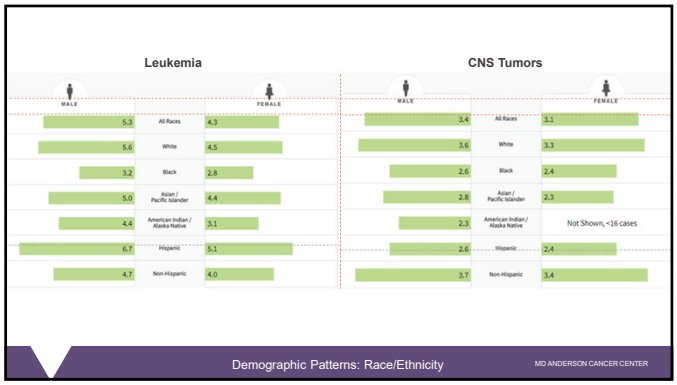

Demographic Patterns: Race/Ethnicity

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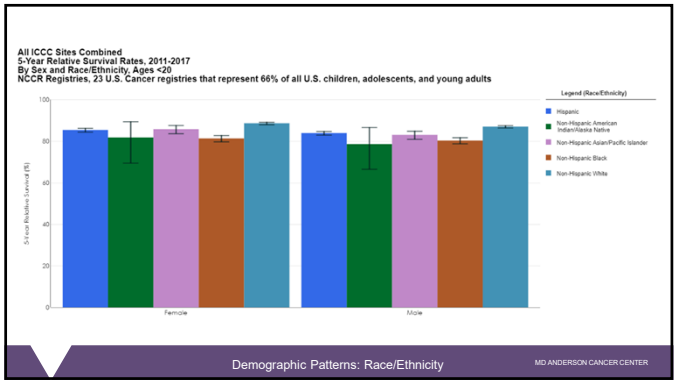

Demographic Patterns: Race/Ethnicity

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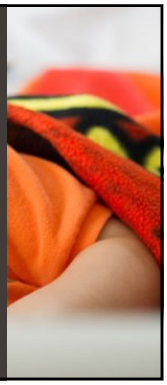
Neuropsychological Outcomes

Non-CNS Cancers



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Number of Childhood Cancer Diagnoses Per Year
Total = 17,293, Age 0-19

- Leukemia: 24%
- Brain and Central Nervous System: 25%
- Neuroblastoma and other peripheral nerve cell tumor: 4%
- Lymphoma and Reticuloendothelial Neoplasms: 15%
- Kidney Tumors (including Wilms Tumor): 3%
- Liver Tumors (including Hepatoblastoma): 1%
- Bone Tumors: 5%
- Rhabdomyosarcoma: 2%
- Retinoblastoma: 2%
- Thyroid Carcinoma: 6%
- Germ Cell Tumors: 5%
- Melanoma: 2%
- Other: 6%

Source: Source: Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2018, National Cancer Institute. Bethesda, MD, (seer.cancer.gov) based on November 2020 SEER data submission, posted to the SEER web site, April 2021.

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Cognitive Outcomes (Non-CNS cancers)

Methodological Issues	General Outcomes

• Understudied
• Often small sample sizes and/or heterogenous samples (varying diagnoses and treatments)
• Emphasis on self-report v. performance-based measures
• Varying methodologies (e.g., instrumentation, timing of evaluations)
• Lacking longitudinal studies
• Role of premorbid functioning and other child/contextual factors unclear
	• Increased cognitive risk but varies across studies
	• From CCSS, SJLIFE, COG studies
	  ○ Attention, memory, processing speed, executive skills, emotional regulation have been most often implicated
	• Co-morbid health conditions (CHCs) as dx/tx effects likely associated with cognition
	  ○ Cardiac (anthracyclines – e.g., doxorubicin)
	  ○ Pulmonary (e.g., methotrexate, Ara-C, bleomycin)
	  ○ Endocrine & obesity (e.g., cyclophosphamide)
	  ○ Hypertension (e.g., cisplatin)
	  ○ Neuropathy (e.g., vincristine, cis/carboplatin, etoposide)
	  ○ Leukoencephalopathy (e.g., methotrexate)
	  ○ Hearing loss (cisplatin, carboplatin)
	  ○ Sleep disruption/fatigue

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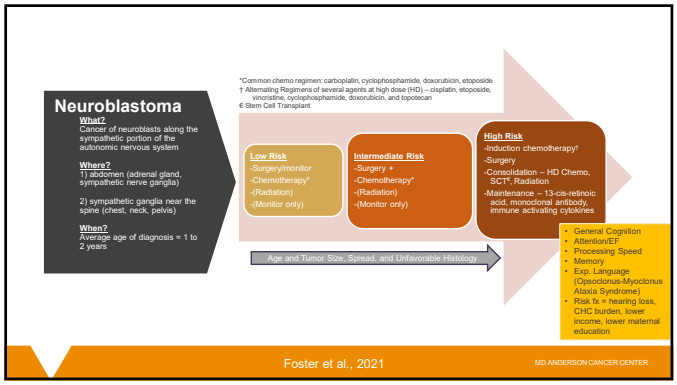
Neuroblastoma
What?
Cancer of neuroblasts along the sympathetic portion of the autonomic nervous system
Where?
1) abdomen (adrenal gland, sympathetic nerve ganglia)
2) sympathetic ganglia near the spine (chest, neck, pelvis)
When?
Average age of diagnosis = 1 to 2 years
*Common chemo regimen: carboplatin, cyclophosphamide, doxorubicin, etoposide
† Alternating Regimens of several agents at high dose (HD) – cisplatin, etoposide, vincristine, cyclophosphamide, doxorubicin, and topotecan
€ Stem Cell Transplant
Low Risk
-Surgery/monitor
-Chemotherapy*
-(Radiation)
-(Monitor only)
Intermediate Risk
-Surgery +
-Chemotherapy*
-(Radiation)
-(Monitor only)
High Risk
-Induction chemotherapy†
-Surgery
-Consolidation – HD Chemo, SCT€, Radiation
-Maintenance – 13-cis-retinoic acid, monoclonal antibody, immune activating cytokines
Age and Tumor Size, Spread, and Unfavorable Histology
General Cognition
Attention/EF
Processing Speed
Memory
Exp. Language (Opsoclonus-Myoclonus Ataxia Syndrome)
Risk fx = hearing loss, CHC burden, lower income, lower maternal education
Foster et al., 2021
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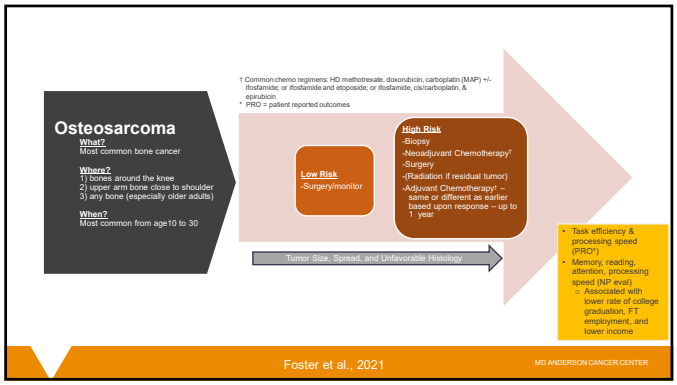
Osteosarcoma
What?
Most common bone cancer
Where?
1) bones around the knee
2) upper arm bone close to shoulder
3) any bone (especially older adults)
When?
Most common from age10 to 30
† Common chemo regimens: HD methotrexate, doxorubicin, carboplatin (MAP) +/- ifosfamide; or ifosfamide and etoposide; or ifosfamide, cis/carboplatin, & epirubicin
* PRO = patient reported outcomes
Low Risk
-Surgery/monitor
High Risk
-Biopsy
-Neoadjuvant Chemotherapy†
-Surgery
-(Radiation if residual tumor)
-Adjuvant Chemotherapy† – same or different as earlier based upon response – up to 1 year
Tumor Size, Spread, and Unfavorable Histology
Task efficiency & processing speed (PRO*)
Memory, reading, attention, processing speed (NP eval)
Associated with lower rate of college graduation, FT employment, and lower income
Foster et al., 2021
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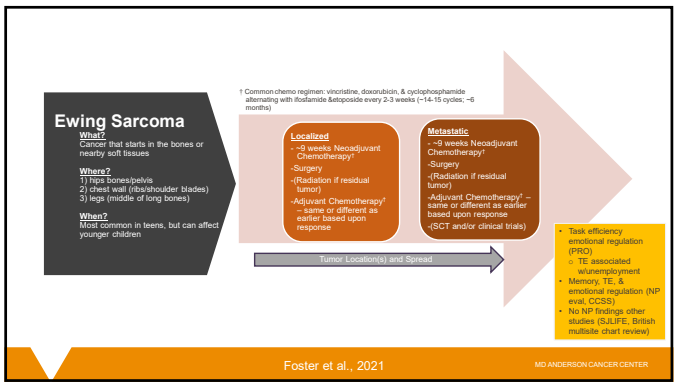
Ewing Sarcoma
What?
Cancer that starts in the bones or nearby soft tissues
Where?
1) hips bones/pelvis
2) chest wall (ribs/shoulder blades)
3) legs (middle of long bones)
When?
Most common in teens, but can affect younger children
† Common chemo regimen: vincristine, doxorubicin, & cyclophosphamide alternating with ifosfamide &etoposide every 2-3 weeks (~14-15 cycles; ~6 months)
Localized
- ~9 weeks Neoadjuvant Chemotherapy†
-Surgery
-(Radiation if residual tumor)
-Adjuvant Chemotherapy† – same or different as earlier based upon response
Metastatic
- ~9 weeks Neoadjuvant Chemotherapy†
-Surgery
-(Radiation if residual tumor)
-Adjuvant Chemotherapy† – same or different as earlier based upon response
-(SCT and/or clinical trials)
Tumor Location(s) and Spread
Task efficiency emotional regulation (PRO)
TE associated w/unemployment
Memory, TE, & emotional regulation (NP eval, CCSS)
No NP findings other studies (SJLIFE, British multisite chart review)
Foster et al., 2021
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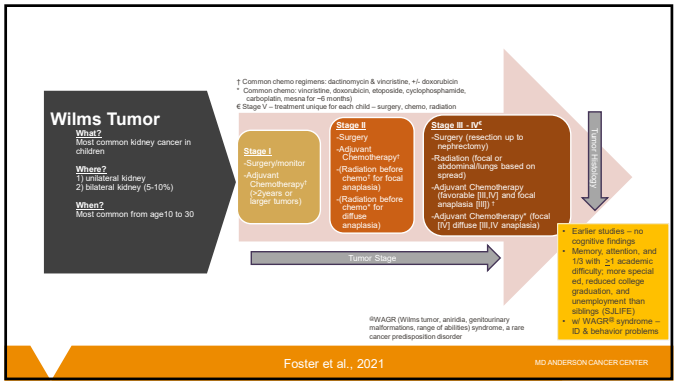
† Common chemo regimens: dactinomycin & vincristine, +/- doxorubicin
* Common chemo: vincristine, doxorubicin, etoposide, cyclophosphamide, carboplatin, mesna for ~6 months)
€ Stage V – treatment unique for each child – surgery, chemo, radiation
Wilms Tumor
What?
Most common kidney cancer in children
Where?
1) unilateral kidney
2) bilateral kidney (5-10%)
When?
Most common from age10 to 30
Stage I
-Surgery/monitor
-Adjuvant Chemotherapy† (>2years or larger tumors)
Stage II
-Surgery
-Adjuvant Chemotherapy*
-(Radiation before chemo* for focal anaplasia)
-(Radiation before chemo* for diffuse anaplasia)
Stage III - IV€
-Surgery (resection up to nephrectomy)
-Radiation (focal or abdominal/lungs based on spread)
-Adjuvant Chemotherapy (favorable [III,IV] and focal anaplasia [III]) †
-Adjuvant Chemotherapy* (focal [IV] diffuse [III,IV anaplasia)
Tumor Response
Tumor Stage
Earlier studies – no cognitive findings
Memory, attention, and 1/3 with ≥1 academic difficulty; more special ed, reduced college graduation, and unemployment than siblings (SJLIFE)
w/ WAGR¶ syndrome – ID & behavior problems
¶WAGR (Wilms tumor, aniridia, genitourinary malformations, range of abilities) syndrome, a rare cancer predisposition disorder
Foster et al., 2021
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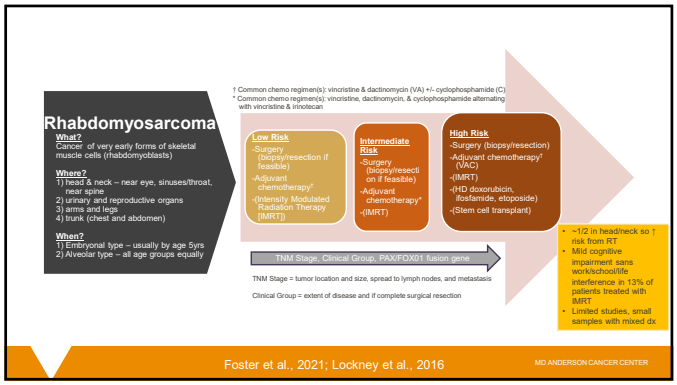
† Common chemo regimen(s): vincristine & dactinomycin (VA) +/- cyclophosphamide (C)
* Common chemo regimen(s): vincristine, dactinomycin, & cyclophosphamide alternating with vincristine & irinotecan
Rhabdomyosarcoma
What?
Cancer of very early forms of skeletal muscle cells (rhabdomyoblasts)
Where?
1) head & neck – near eye, sinuses/throat, near spine
2) urinary and regroductive organs
3) arms and legs
4) trunk (chest and abdomen)
When?
1) Embryonal type – usually by age 5yrs
2) Alveolar type – all age groups equally
Low Risk
-Surgery (biopsy/resection if feasible)
-Adjuvant chemotherapy*
-(Intensity Modulated Radiation Therapy [IMRT])
Intermediate Risk
-Surgery (biopsy/resection if feasible)
-Adjuvant chemotherapy*
-(IMRT)
High Risk
-Surgery (biopsy/resection)
-Adjuvant chemotherapy* (VAC)
-(IMRT)
-(HD doxorubicin, ifosfamide, etoposide)
-(Stem cell transplant)
TNM Stage, Clinical Group, PAX/FOX01 fusion gene
TNM Stage = tumor location and size, spread to lymph nodes, and metastasis
Clinical Group = extent of disease and if complete surgical resection
~1/2 in head/neck so ↑ risk from RT
Mild cognitive impairment sans work/school/life interference in 13% of patients treated with IMRT
Limited studies, small samples with mixed dx
Foster et al., 2021; Lockney et al., 2016
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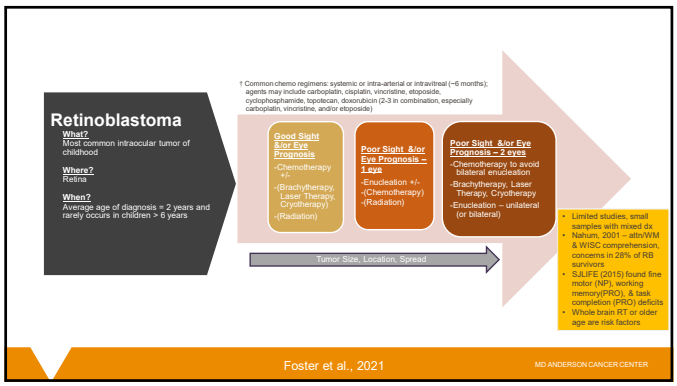
† Common chemo regimens: systemic or intra-arterial or intravitreal (~6 months); agents may include carboplatin, cisplatin, vincristine, etoposide, cyclophosphamide, topotecan, doxorubicin (2-3 in combination, especially carboplatin, vincristine, and/or etoposide)
Retinoblastoma
What?
Most common intraocular tumor of childhood
Where?
Retina
When?
Average age of diagnosis = 2 years and rarely occurs in children > 6 years
Good Sight &/or Eye Prognosis
-Chemotherapy +/-
-(Brachytherapy, Laser Therapy, Cryotherapy)
-(Radiation)
Poor Sight &/or Eye Prognosis – 1 eye
-Enucleation +/-
-(Chemotherapy)
-(Radiation)
Poor Sight &/or Eye Prognosis – 2 eyes
-Chemotherapy to avoid bilateral enucleation
-Brachytherapy, Laser Therapy, Cryotherapy
-Enucleation – unilateral (or bilateral)
Tumor Size, Location, Spread
Limited studies, small samples with mixed dx
Nahum, 2001 – attn/WM & WISC comprehension, concerns in 28% of RB survivors
SJLIFE (2015) found fine motor (NP), working memory(PRO), & task completion (PRO) deficits
Whole brain RT or older age are risk factors
Foster et al., 2021
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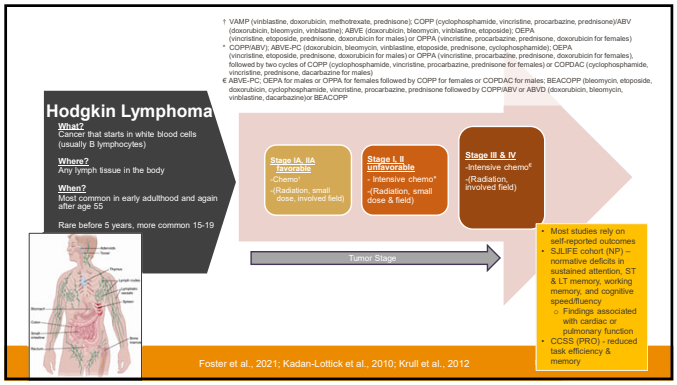
† VAMP (vinblastine, doxorubicin, methotrexate, prednisone); COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABV (doxorubicin, bleomycin, vinblastine); ABVE (doxorubicin, bleomycin, vinblastine, etoposide); OEPA (vincristine, etoposide, prednisone, doxorubicin for males) or OPPA (vincristine, procarbazine, prednisone, doxorubicin for females)
* COPP/ABV); ABVE-PC (doxorubicin, bleomycin, vinblastine, etoposide, prednisone, cyclophosphamide); OEPA (vincristine, etoposide, prednisone, doxorubicin for males) or OPPA (vincristine, procarbazine, prednisone, doxorubicin for females), followed by two cycles of COPP (cyclophosphamide, vincristine, procarbazine, prednisone for females) or COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine for males)
€ ABVE-PC; OEPA for males or OPPA for females followed by COPP for females or COPDAC for males; BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone followed by COPP/ABV or ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)or BEACOPP
Hodgkin Lymphoma
What?
Cancer that starts in white blood cells (usually B lymphocytes)
Where?
Any lymph tissue in the body
When?
Most common in early adulthood and again after age 55
Rare before 5 years, more common 15-19
Stage IA, IIA favorable
-Chemo†
-(Radiation, small dose, involved field)
Stage I, II unfavorable
- Intensive chemo*
-(Radiation, small dose & field)
Stage III & IV
-Intensive chemo€
-(Radiation, involved field)
Tumor Stage
Most studies rely on self-reported outcomes
SJLIFE cohort (NP) – normative deficits in sustained attention, ST & LT memory, working memory, and cognitive speed/fluency
Findings associated with cardiac or pulmonary function
CCSS (PRO) - reduced task efficiency & memory
Foster et al., 2021; Kadan-Lottick et al., 2010; Krull et al., 2012

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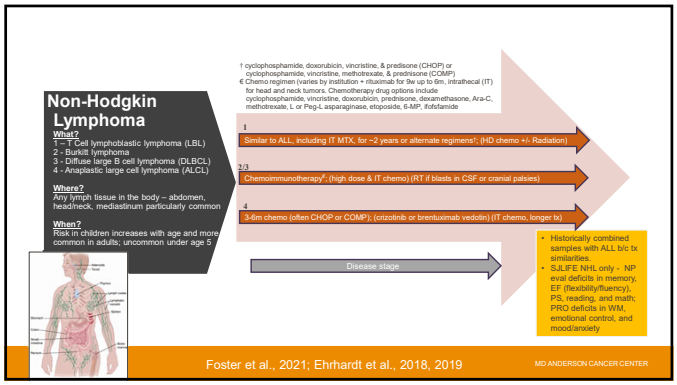
† cyclophosphamide, doxorubicin, vincristine, & predisone (CHOP) or cyclophosphamide, vincristine, methotrexate, & predisone (COMP)
€ Chemo regimen (varies by institution + rituximab for 9w up to 6m, intrathecal (IT) for head and neck tumors. Chemotherapy drug options include cyclophosphamide, vincristine, doxorubicin, prednisone, dexamethasone, Ara-C, methotrexate, L or Peg-L asparaginase, etoposide, 6-MP, ifosfamide
Non-Hodgkin Lymphoma
What?
1 – T Cell lymphoblastic lymphoma (LBL)
2 - Burkitt lymphoma
3 - Diffuse large B cell lymphoma (DLBCL)
4 - Anaplastic large cell lymphoma (ALCL)
Where?
Any lymph tissue in the body – abdomen, head/neck, mediastinum particularly common
When?
Risk in children increases with age and more common in adults; uncommon under age 5
1
Similar to ALL, including IT MTX, for ~2 years or alternate regimens†; (HD chemo +/- Radiation)
2/3
Chemoimmunotherapy€; (high dose & IT chemo) (RT if blasts in CSF or cranial palsies)
4
3-6m chemo (often CHOP or COMP); (crizotinib or brentuximab vedotin) (IT chemo, longer tx)
Disease stage
Historically combined samples with ALL b/c tx similarities.
SJLIFE NHL only - NP eval deficits in memory, EF (flexibility/fluency), PS, reading, and math; PRO deficits in WM, emotional control, and mood/anxiety
Foster et al., 2021; Ehrhardt et al., 2018, 2019
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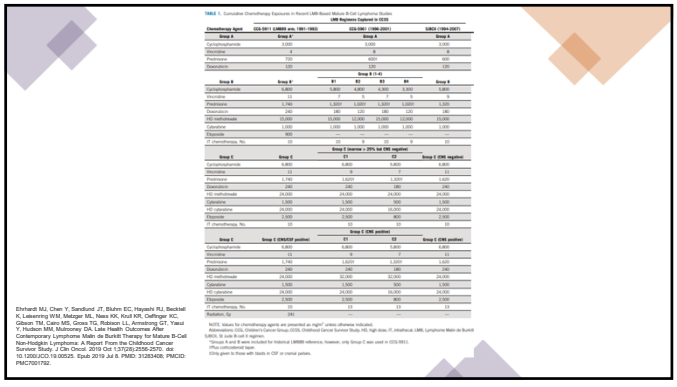
Ehrhardt MJ, Chen Y, Sandlund JT, Bluhm EC, Hayashi RJ, Beckhelling K, Leisenring WM, Metzger ML, Naeu KK, Krull KR, Oeffinger KC, Gibson TM, Cairo MS, Gross TG, Robison LL, Armstrong GT, Yasui Y, Hudson MM, Mahoney DH. Late Health Outcomes After Contemporary Lymphome Malin de Burkitt Therapy for Mature B-Cell Non-Hodgkin Lymphoma: A Report From the Childhood Cancer Survivor Study. J Clin Oncol. 2019 Oct 1;37(28):2556-2570. doi: 10.1200/JCO.19.00525. Epub 2019 Jul 9. PMID: 31283408; PMCID: PMC7001792.

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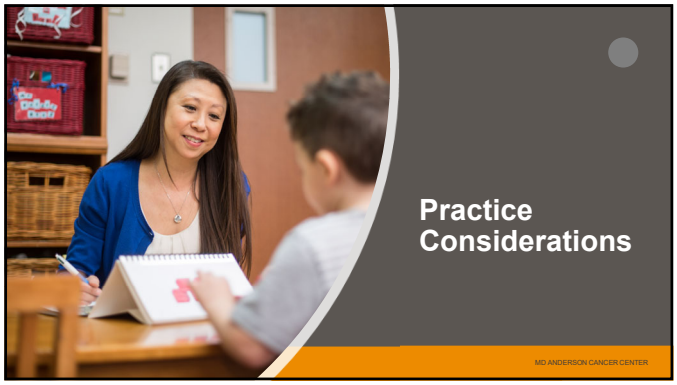
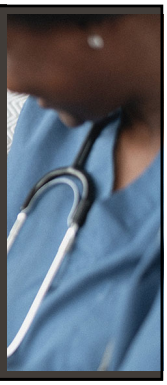


25

Neuropsychological Outcomes

Acute Lymphoid Leukemia



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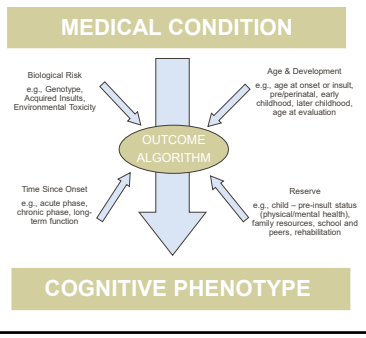
Cognitive Outcome Model

Dennis, 2000



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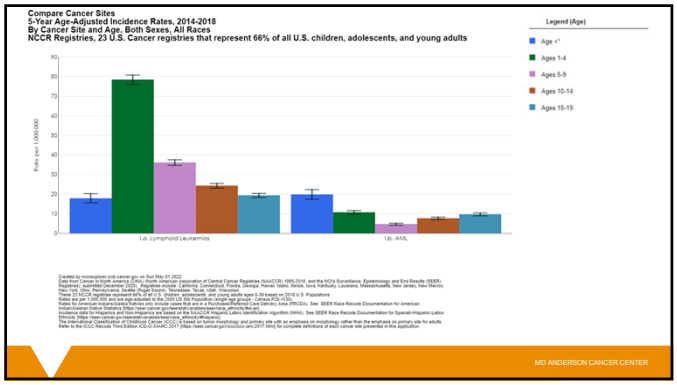

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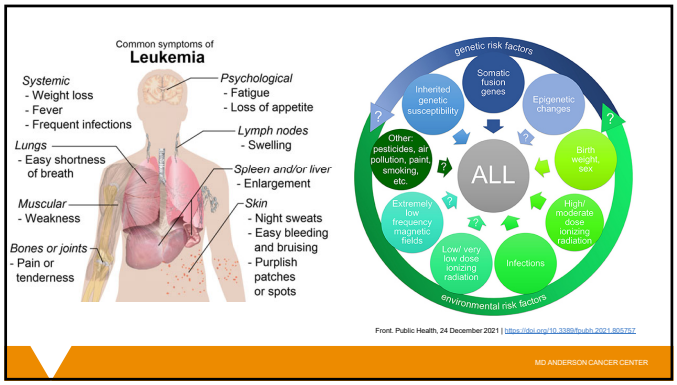

Front. Public Health, 24 December 2021 | https://doi.org/10.3389/fpubh.2021.805757

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Acute Lymphocytic/Lymphoblastic Leukemia (ALL)

Childhood ALL Subtypes

- Surface Proteins
  - B-Cell ALL
  - T-Cell ALL
- Genetic Changes
  - Philadelphia Chromosome-Positive ALL
  - Philadelphia Chromosome-like (Ph-like) ALL

Risk Stratification Factors

- B cell or T cell (T cell higher risk, racial disparities)
- Cytogenetic abnormalities (variable)
- Age at dx (10+ = high risk, <1 very high risk)
- Initial WBC count (higher WBC = higher risk)
- CNS involvement
- Testicular involvement
- Induction response (remission after 1-2 weeks lower risk)
- Minimal Residual Disease (MRD)
- Biological sex (females possibly better cure rate)

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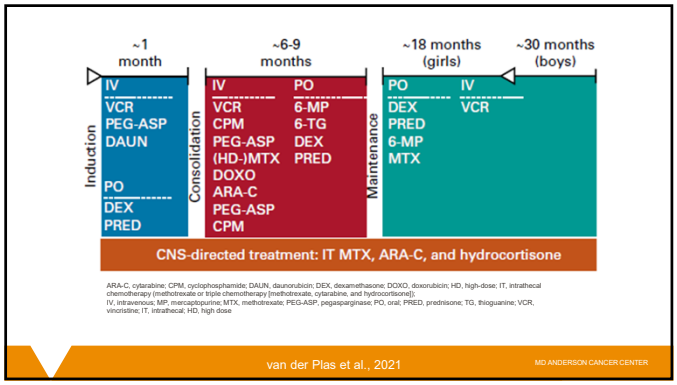
~1 month
~6-9 months
~18 months (girls)
~30 months (boys)
Induction
IV
VCR
PEG-ASP
DAUN
PO
DEX
PRED
Consolidation
IV
VCR
CPM
PEG-ASP
(HD-)MTX
DOXO
ARA-C
PEG-ASP
CPM
PO
6-MP
6-TG
DEX
PRED
Maintenance
PO
DEX
PRED
6-MP
MTX
IV
VCR
CNS-directed treatment: IT MTX, ARA-C, and hydrocortisone
ARA-C, cytarabine; CPM, cyclophosphamide; DAUN, daunorubicin; DEX, dexamethasone; DOXO, doxorubicin; HD, high-dose; IT, intrathecal chemotherapy (methotrexate or triple chemotherapy [methotrexate, cytarabine, and hydrocortisone]); IV, intravenous; MP, mercaptopurine; MTX, methotrexate; PEG-ASP, pegaspargrinase; PO, oral; PRED, prednisone; TG, thioguanine; VCR, vincristine; IT, intrathecal; HD, high dose
van der Plas et al., 2021
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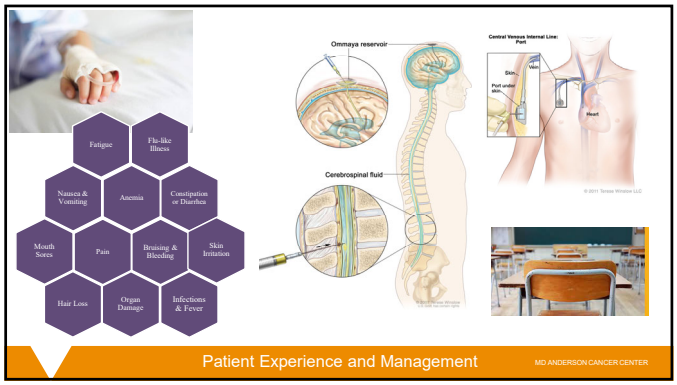
Fatigue
Flu-like Illness
Nausea & Vomiting
Anemia
Constipation or Diarrhea
Mouth Sores
Pain
Bruising & Bleeding
Skin Irritation
Hair Loss
Organ Damage
Infections & Fever
Ommaya reservoir
Cerebrospinal fluid
Central Venous Internal Line: Port
Skin
Port under skin
Vein
Heart
Patient Experience and Management
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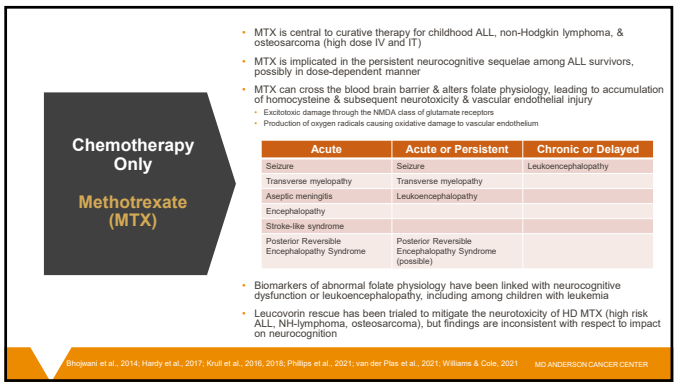
Chemotherapy Only
Methotrexate (MTX)
MTX is central to curative therapy for childhood ALL, non-Hodgkin lymphoma, & osteosarcoma (high dose IV and IT)
MTX is implicated in the persistent neurocognitive sequelae among ALL survivors, possibly in dose-dependent manner
MTX can cross the blood brain barrier & alters folate physiology, leading to accumulation of homocysteine & subsequent neurotoxicity & vascular endothelial injury
Excitotoxic damage through the NMDA class of glutamate receptors
Production of oxygen radicals causing oxidative damage to vascular endothelium
Acute
Acute or Persistent
Chronic or Delayed
Seizure
Seizure
Leukoencephalopathy
Transverse myelopathy
Transverse myelopathy
Aseptic meningitis
Leukoencephalopathy
Encephalopathy
Stroke-like syndrome
Posterior Reversible Encephalopathy Syndrome
Posterior Reversible Encephalopathy Syndrome (possible)
Biomarkers of abnormal folate physiology have been linked with neurocognitive dysfunction or leukoencephalopathy, including among children with leukemia
Leucovorin rescue has been trialed to mitigate the neurotoxicity of HD MTX (high risk ALL, NH-lymphoma, osteosarcoma), but findings are inconsistent with respect to impact on neurocognition
Bhojwani et al., 2014; Hardy et al., 2017; Krull et al., 2016, 2018; Phillips et al., 2021; van der Plas et al., 2021; Williams & Cole, 2021
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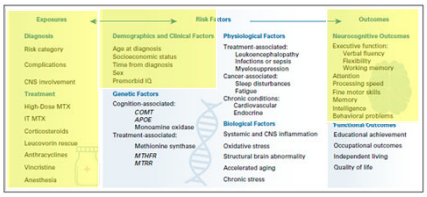
Chemotherapy Only

Neurocognitive Outcomes



Campbell et al., 2007; Peterson et al., 2008; van der Plas et al., 2021; Zhou et al., 2020

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Chemotherapy-Only: Disease, Treatment, & Demographic Factors

	van der Plas et al. (2021)	Jacola et al. (2016)	Hardy et al. (2017)	Partanen et al. (2021)
Sample	CCSS; ≥ 5y post dx; <21 at dx and ≥18 at eval; n=1207 ALL & n=2273 sibling controls (SC)	n=339, single risk stratified protocol (St. Jude Total XV)	n=192; ≤ 18 at dx; single treatment protocol (AALL0232)	n=233; single risk-stratified protocol (St. Jude Total XV)
Design	Retrospective, multi-institutional, survey-based (CCSS-NCQ); impairment ≥90th %tile	Prospective, longitudinal @ induction, EOT, & 2y post EOT; full NP battery and caregiver ratings	Prospective, cross-sectional between 8-24m post EOT; screening battery (IQ, WM, PS)	Prospective, longitudinal; LCA to study individual change (4 time points induction to 2y post EOT); NP (attn, memory) and caregiver ratings
Neurocognition (NC) & Risk Factors	▪ ALL increased prevalence of task efficiency & memory impairment v. SC ▪ NC associated w/ higher MTX dose, exposure to dexamethasone, & chronic health conditions (CHC's)* in sex-specific manner **Female Gender** **Younger Age** **Higher Tx intensity** **Dexamethasone?** **↑ Time Since Treatment** **Low SES**	▪ Elevated risk attention problems overall v. norms at final time point, EOT attention predicted academics 2 years later ▪ Increased risk with higher-intensity CNS directed chemo, younger age at dx, and males on various neurocognitive skills	▪ No association between NC & MTX delivery (HDMTX w/ leucovorin rescue v. escalating dose MTX) or NC & corticosteroid (dexamethasone v. prednisone) ▪ < 10 years @ dx greatest risk (IQ, PS) ▪ SES (proxy measure public insurance) risk for lower IQ	▪ Most patients stable (below to above average) ▪ 3-6% patients decline; risks include female sex, sepsis, and older age ▪ 3-11% improve; risks include low "baseline" IQ

*CHCs associated with outcomes = neurologic, pulmonary, and endocrine

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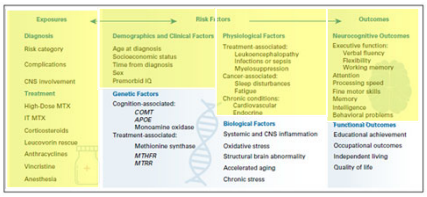
Chemotherapy Only

Neurocognitive Outcomes



van der Plas et al., 2021; Cheung et al., 2016, 2018

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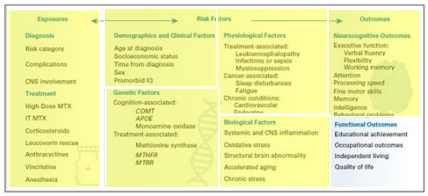
Chemotherapy Only

Neurocognitive Outcomes



- Inflammation – MTX & other chemotherapy agents are associated with increased cytokines (proinflammatory markers), which have been associated with neurocognitive impairment in childhood ALL and other adult cancers
- Genetic polymorphisms – variant forms of a specific DNA sequence
  - Can be predisposing to cognitive impairment and accelerate onset of neurocognitive sequelae in children treated for ALL.
  - Can influence pharmacokinetics of chemotherapy agents, ultimately leading to neurotoxicity.

van der Plas et al., 2021; Cheung et al., 2016, 2018

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Table 2. Frequency of Targeted Pathway Polymorphisms Examined As Mediators of Neurocognitive Outcomes

Gene	Gene Description	Gene Function	Genomic Variation	Minor Allele Frequency (%)	Survivor Population Studied	Findings
MTR	Methionine synthase	Regeneration of methionine from homocysteine; polymorphisms result in excess homocysteine	A2756G	22	ALL	Increased risk of attention problems[40,80]
MTHFR	Methylenetetrahydrofolate reductase	Catalyzes production of circulating folate; polymorphisms result in lower folate concentration	A1298C	25	ALL	Increased risk of attention problems and executive dysfunction[79,81]
GSTP1	Glutathione S-transferase	Catalyzes glutathione conjugation of products of reactive oxidation and sequesters steroids; polymorphisms result in increased susceptibility to oxidative stress	G313A	35	ALL	Increased risk for attention problems[40,80]
GSTT1			GSTT1*0	5	ALL	Increased risk for attention problems[40]
APOE4	Apolipoprotein E	Metabolizes lipoproteins; polymorphisms increase risk for vascular disease and Alzheimer's	Cys112Arg	15	ALL	Increased risk for attention problems[40]
COMT	Catechol-O-methyltransferase	Inactivates catecholamine neurotransmitters such as dopamine, epinephrine, and norepinephrine; polymorphisms result in excess extracellular dopamine	Val158Met	37	ALL, CNS tumor	Increased risk for neurocognitive impairment in CNS tumor[40,80]
MAOA	Monoamine oxidase A	Breaks down amine neurotransmitters such as dopamine, norepinephrine, and serotonin; polymorphisms result in excess extracellular neurotransmitter concentrations	T1460C	45	ALL	Increased risk for attention problems[50]

Abbreviation: ALL, acute lymphoblastic leukemia.

Krull et al., 2018

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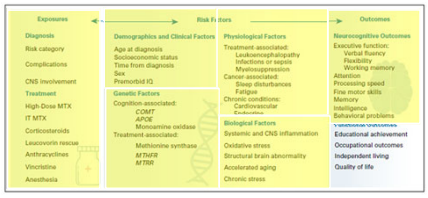
Chemotherapy Only

Neurocognitive Outcomes



- Other potential genetic risk factors might include:
  - Telomere shortening, which may be impacted by environmental exposures like chronic stress as well as treatment exposures
  - Epigenetics – how behaviors/environment can cause changes in gene expressions without changing DNA sequence

van der Plas et al., 2021; Williams & Cole, 2021;

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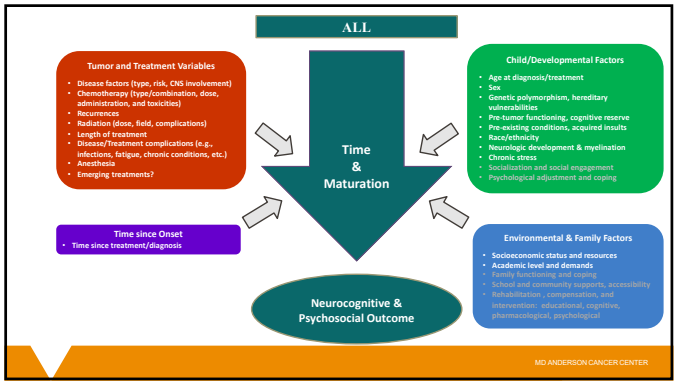

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Stem Cell Transplant (SCT)

High Risk ALL
Poor Treatment Response
Relapse

Goal: cure the cancer by destroying the cancer cells in the bone marrow with HD chemotherapy and then replace with new, healthy blood-forming stem cells

Neurocognitive

- With TBI + cranial/craniospinal RT conditioning, 38% showed post-SCT decreases in processing speed and/or working memory (Hiniker et al., 2014)
- At median 5y post-tx, HR-ALL patients treated with SCT showed lower white matter and gray matter brain volumes + lower cognitive performance compared to 2 comparison groups (Zajac-Spychala et al., 2020):
  - HR-ALL patients treated with the same HD chemo and CRT dose
  - Newly diagnosed ALL patients

Hiniker et al., 2014

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Chimeric Antigen Receptor (CAR) T-Cell Therapy

Relapsed/Refractory ALL
Non-Hodgkin Lymphoma

Leukemia & Lymphoma Society (lls.org)

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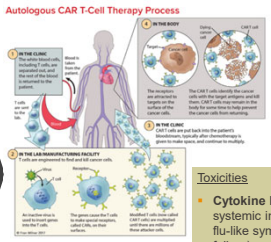
Chimeric Antigen Receptor (CAR) T-Cell Therapy

Relapsed/Refractory ALL Non-Hodgkin Lymphoma



Toxicities

- **Cytokine Release Syndrome** – systemic inflammatory response (e.g., flu-like symptoms up to multiorgan failure)
- **Immune Effector Cell-Associated Neurotoxicity Syndrome** (ICANS; e.g., confusion, expressive aphasia, obtundation, myoclonus, and seizure)

Leukemia & Lymphoma Society (lls.org); Ruark et al., 2020 MD ANDERSON CANCER CENTER

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Chimeric Antigen Receptor (CAR) T-Cell Therapy

Relapsed/Refractory ALL Non-Hodgkin Lymphoma

Outcomes

- Between 1 to 4 years post-treatment, adults treated for various leukemias or non-Hodgkin lymphoma self-reported (PROMIS) overall good outcomes, but (Ruark et al., 2020):
  - 37.5% reported cognitive problems and ~50% reported at least one meaningful neuropsychiatric outcome (anxiety, depression, cognition)
  - Trend for association between acute neurotoxicity and cognition
- In a sample of relapsed ALL patients (mean age 13.8), 7/11 had CRS and 4/11 had ICANS
  - All patients had global thinning of cortex pre-CAR T-cell therapy, likely related to prior treatment regimens
  - Worse baseline thinning and worse baseline NP (attention, WM) were associated with development of ICANS with CAR T-cell therapy
  - Patients with ICANS developed additional cortical thinning that resolved in all but a subset of patients

Ruark et al., 2020; Taraseviciute et al., 2020 MD ANDERSON CANCER CENTER

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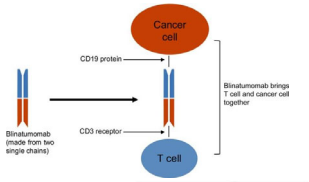
Other Emerging Treatments

Blinatumomab

Blinatumomab (relapsed/refractory ALL; MRD+ disease B-ALL)



Blinatumomab, a type of immunotherapy, binds to certain molecules on leukemia cells and T cells, bringing the T cells close enough to the leukemia cells to kill them.
Credit: Clin Pharmacol Ther. 2019 Oct. doi: 10.1002/cpt.1596 (CC BY-NC 4.0)

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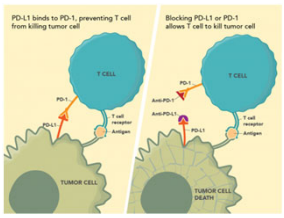
Other Emerging Treatments

Nivolumab

Nivolumab (relapsed/refractory ALL)



https://www.fda.gov/drugs/regulatory-science-action/impact-story-determining-clinical-benefit-treatment-beyond-progression-immune-checkpoint-inhibitors

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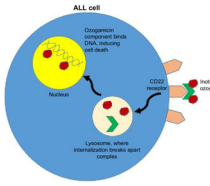
Other Emerging Treatments

Inotuzumab ozogamicin



Inotuzumab
(relapsed/refractory ALL)

- Form of monoclonal antibody treatment
- Selective in nature, binding to receptors that are highly expressed on cancer cells and less so on normal cells
- Targets the surface antigen CD22, which is expressed on leukemic blasts in >90% of B-cell ALL patients
- Clinical trials as single-agent and in combo with low dose chemo

Yurkiewicz IR, Muffly L, Liedtke M. Inotuzumab ozogamicin: a CD22 mAb-drug conjugate for adult relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Drug Des Devel Ther. 2018 Jul 24;12:2293-2300. doi: 10.2147/DDDT.S150317. PMID: 30087554; PMCID: PMC6063246.

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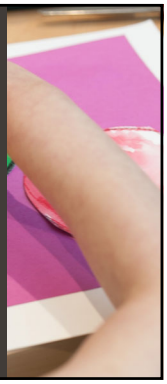
Neuropsychological Outcomes

Brain Tumors



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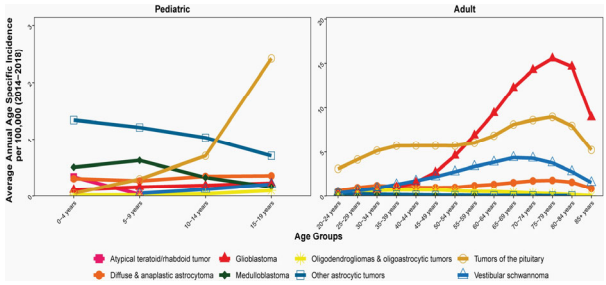
Pediatric Brain Tumors



Neuro Oncol, Volume 23, Issue Supplement_3, October 2021, Pages iii1–iii105, https://doi.org/10.1093/neuonc/noab200

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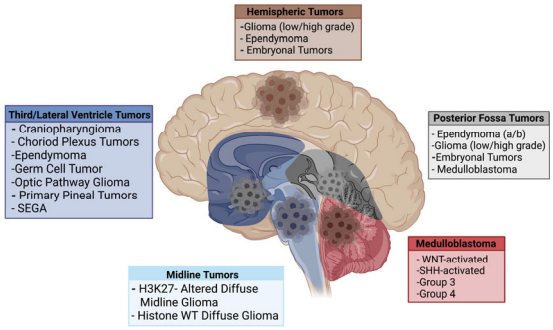

Power, E. A., Rechberger, J. S., Gupta, S., Schwartz, J. D., Daniels, D. J., & Khatua, S. (2022). Drug Delivery Across the Blood-Brain Barrier for the Treatment of Pediatric Brain Tumors–An Update. Advanced Drug Delivery Reviews, 114303.

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Brain Tumor Types, Common Locations, & Usual Treatments

Astrocytoma (low grade)	Cerebellum, cerebral hemispheres	Surgery
Astrocytoma (high grade)	Cerebral hemispheres, brainstem	Surgery, chemo, RT
Atypical Teratoid/Rhabdoid (ATRT)	Any location	Surgery, chemo, RT
Brainstem glioma (low grade)	Brainstem	Observation; surgery, RT
Brainstem glioma (high grade)	Brainstem	Radiation, chemo
Optic glioma	Optic nerves	Observation; chemo; RT; surgery less common

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Brain Tumor Types, Locations, & Common Treatments

Craniopharyngioma	Suprasellar region (hypothalamus, pituitary, optic chiasm)	Surgery; observation, RT
Ependymoma	Ventricles; 4th ventricle	Surgery; observation, RT; chemo less common
Germ Cell Tumor	Pineal region; suprasellar	Surgery, RT, chemo
Medulloblastoma	Posterior Fossa	Surgery, RT, chemo
Primitive Neuroectodermal Tumor (PNET)	Cerebral hemispheres; any location	Surgery, chemo, RT

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Molecular subtyping: Medulloblastoma

Subgroup	WNT	SHH	Group 3	Group 4
Clinical Characteristics				
% of Cases	10	30	25	35
Age at Diagnosis				
Gender Ratio (M:F)	1:1	1:1	2:1	3:1
Anatomic Location				
Histology	Classic, Rarely LCA	Desmoplastic, Classic, LCA	Classic, LCA	Classic, LCA
Metastasis at Diagnosis (%)	5-10	15-20	40-45	35-40
Recurrence Pattern	Rare; Local or metastatic	Local	Metastatic	Metastatic
Prognosis	Very good	Infants good, others intermediate	Poor	Intermediate
Molecular Characteristics				
Proposed Cell of Origin	Progenitor cells in the lower rhombic lip	Granule precursors or the external granule layer	Neural stem cells	Unipolar brush cells
Recurrent Gene Amplifications	-	*MYCN* *GLI1 or GLI2*	*MYC* *MYCN* *OTX2*	*SNCAIP* *MYCN* *OTX2* *CCNB*
Recurrent SNVs	*CTNNB1* *DDX3X* *SMARCA4* *TP53*	*PTCH1* *TERT* *SUFU* *SMO* *TP53*	*SMARCA4* *KBTBD4* *CTDNEP1* *KMT2D*	*KDM6A* *ZMYM3* *KTM2C* *KBTBD4*
Cytogenetic Events ■ Gain ■ Loss	6	3q, 9p 9q, 10q, 17p	1q, 7, 18 8, 10q, 11, 16q i17q	7, 18q 8, 11p, X i17q
Other Recurrent Genetic Events	-	-	*GFI1* and *GFI1B* enhancer hijacking	*PRDM6*, *GFI1*, and *GFI1B* enhancer hijacking

Age: Infant Child Adult

Juraschka, K., & Taylor, M. D. (2019). Medulloblastoma in the age of molecular subgroups: A review. JNSPG 75th Anniversary invited review article. Journal of Neurosurgery: Pediatrics, 24(4), 353-363.

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2021 WHO CNS Tumor Taxonomy

- Pediatric-type diffuse low-grade gliomas
  - Diffuse astrocytoma, *MYB*- or *MYBL1*-altered
  - Angiocentric glioma
  - Polymorphous low-grade neuroepithelial tumor of the young
  - Diffuse low-grade glioma, MAPK pathway-altered
- Pediatric-type diffuse high-grade gliomas
  - Diffuse midline glioma, H3 K27-altered
  - Diffuse hemispheric glioma, H3 G34-mutant
  - Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
  - Infant-type hemispheric glioma
- Circumscribed astrocytic gliomas
  - Pilocytic astrocytoma
  - High-grade astrocytoma with piloid features
  - Pleomorphic xanthoastrocytoma
  - Subependymal giant cell astrocytoma
  - Chordoid glioma
  - Astroblastoma, *MN1*-altered
- Embryonal tumors
  - Medulloblastoma
    - Medulloblastomas, molecularly defined
      - Medulloblastoma, WNT-activated
      - Medulloblastoma, SHH-activated and *TP53*-wildtype
      - Medulloblastoma, SHH-activated and *TP53*-mutant
      - Medulloblastoma, non-WNT/non-SHH
    - Medulloblastomas, histologically defined
  - Other CNS embryonal tumors
    - Atypical teratoid/rhabdoid tumor
    - *Cribriform neuroepithelial tumor*
    - Embryonal tumor with multilayered rosettes
    - CNS neuroblastoma, *FOXR2*-activated
    - CNS tumor with *BCOR* internal tandem duplication
    - CNS embryonal tumor

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World Health Organization CNS Tumor Grades (2021 Revision)

- Grades 1-4 (Previously grades I-IV)
- Previously, grading was assigned according to natural history (survival times) –grade I considered much more benign than Grade IV
- Now, grading reflects biological similarities within tumor types (rather than clinical behavior)
- May lead to confusion compared to the older system; new system conforms to WHO grading of non-CNS tumors

E.g., WNT-activated medulloblastoma: aggressive if left untreated but responsive to current therapeutic regimens such that nearly all patients have long-term survival. Designated CNS WHO grade 4; equivalent to many untreatable pediatric brain tumors with a poor outcome

55

Brain Tumor Predisposition Factors

Genetic:

- Neurofibromatosis, Type 1 & Type 2
- Li-Fraumeni Syndrome
- von Hippel Lindau Syndrome
- Fanconi anemia
- Tuberous Sclerosis
- Lynch Syndrome
- Gorlin Syndrome

Genetic syndromes account for <5% of pediatric brain tumors

Environmental:

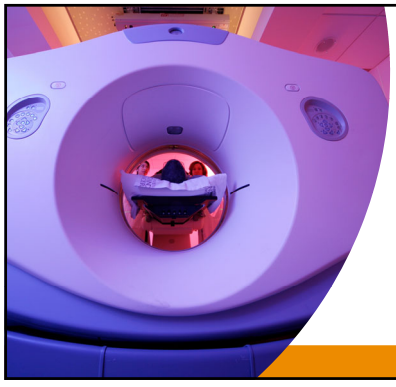
- Previous Radiation to the Brain (dose effect, younger age at exposure increases risk)

Structural:

- Birth defects affecting CNS; neurological anomalies

For review see: Ostrom, Q. T., Adel Fahmideh, M., Cote, D. J., Muskens, I. S., Schraw, J. M., Scheurer, M. E., & Bondy, M. L. (2019). Risk factors for childhood and adult primary brain tumors. Neuro-oncology, 21(11), 1357-1375.

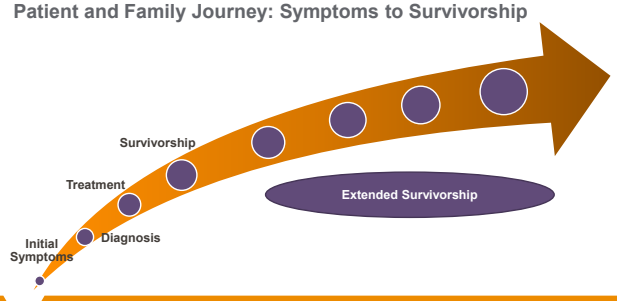
56



Diagnosis, Treatment, & Patient Experience

57

Patient and Family Journey: Symptoms to Survivorship



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Diagnosis, Treatment, & the Patient Experience

Presenting symptoms observed in ER

Headache	67%	Neck/back pain	16%
Hydrocephalus	57%	Papilledema	13%
Nausea/vomiting	49%	Sensory deficits	8%
Gait disturbance	42%	Focal motor weakness	7%
Vision changes	21%	Ptosis	6%
Seizure	17%	Macrocephaly	5%
Behavior / school change	17%	Asymptomatic	3%
Cranial nerve deficits	16%	Unequal pupil size	1%
Altered mental status	16%		

Lanphear, J. & Semark, S. (2014). Presenting symptoms of pediatric brain tumors diagnosed in the emergency department. Pediatric Emergency Care, 30(2), 77-80.

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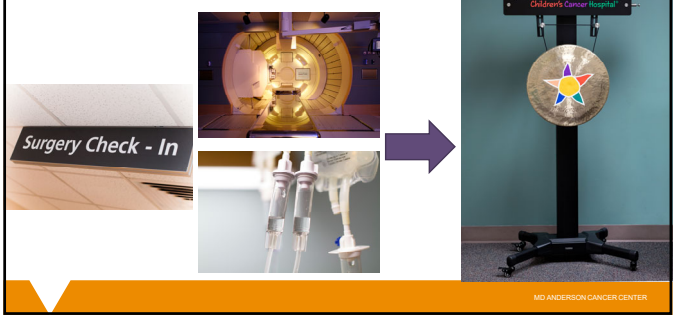
Diagnosis, Treatment, & Patient Experience



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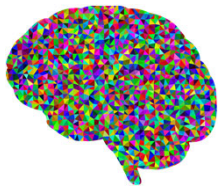
Diagnosis, Treatment, & Patient Experience: Surgery

- Biopsy: Small portion removed and used for diagnostics
- Partial resection: Only part of the tumor removed
- Subtotal resection: Large portions of the tumor removed
- Near total resection: Most of the visible tumor removed
- Gross total resection: The entire tumor that could be seen removed; microscopic cells may remain



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Diagnosis, Treatment, & Patient Experience: Surgery

Surgery Risks & Complications

- Infection
- Stroke
- Seizures
- Repeated anesthesia
- Paresis and paralysis
- Ataxia
- Visual field deficits
- Posterior fossa syndrome
- Hospitalization

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Diagnosis, Treatment, & Patient Experience: Surgery

Posterior Fossa Syndrome (PFS) aka Cerebellar Mutism

- Occurs in up to 31% of children with infratentorial tumors
- Attributed to disruption of cerebello-thalamo-cerebral pathways
- Symptoms emerge approximately 24–48h after surgery, & include diminished speech, ataxia, dysphagia, emotional/behavioral lability and apathy
- Speech and neurologic sequelae often improve with time and rehabilitation
- Recent evidence suggests worse overall neurocognitive outcomes for PBT survivors who experienced posterior fossa syndrome relative to those who did not
- In medulloblastoma, Molecular subgroups 3 & 4 are at highest risk

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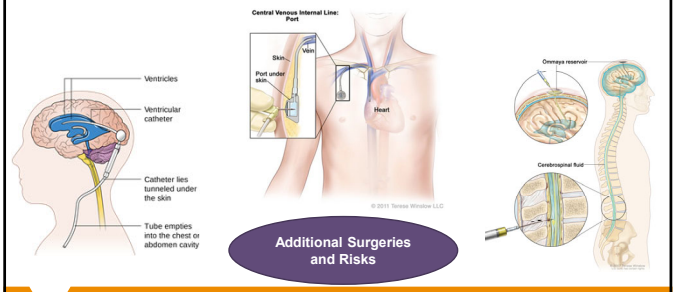
Diagnosis, Treatment, & Patient Experience: Surgery



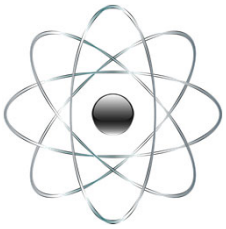
64

65

Diagnosis, Treatment, & Patient Experience: Radiation Therapy

Scope: Focal, Whole Brain, Craniospinal

- 3D Conformal (3D-CRT)
- Intensity modulated radiation therapy (IMRT)
- Volumetric-modulated arc therapy (VMAT)
- Stereotactic radiation therapy (SRT)
- Image-guided radiation therapy (IGRT)
- Particle therapy (Protons)



66

Radiation Side/Late Effects

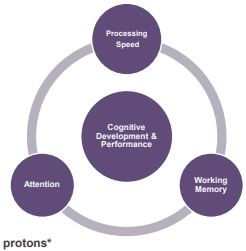
- Alopecia
- Fatigue
- Skin irritation
- Low blood counts
- Nausea
- Mouth sores, dry mouth
- Etc.
- Ototoxicity
- Cataracts
- Skeletal problems
- Cerebrovascular disease
- Secondary neoplasms
- Growth hormone deficiency
- Primary Hypothyroidism
- Central Hypothyroidism
- Hypogonadism and early puberty
- Panhypopituitarism
- Diabetes insipidus

Neurocognitive difficulties

67

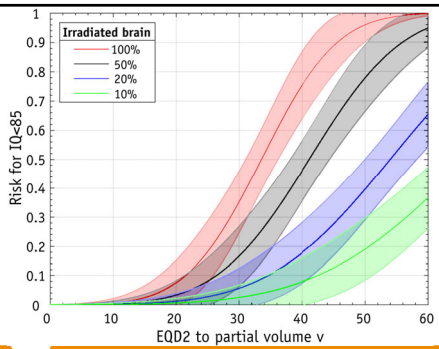
Pathophysiology of Radiation Effects on Cognition

- RT affects microglial and microvascular environments
- Neuroinflammatory responses
- White matter integrity affected
- Hippocampal damage
- Neurogenesis affected
- Observable necrosis in a small number of cases
- Early evidence suggests improved cognitive outcomes with protons*



*Yahya, N., & Mersin, H. A. (2021). Neurocognitive impairment following proton therapy for paediatric brain tumour: a systematic review of post-therapy assessments. Supportive Care in Cancer, 29(6), 3035-3047.

68



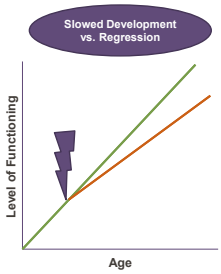
RT Dose & Volume Effects

Mahajan, A., Stavinoha, P. L., Rongthong, W., Brodin, N. P., McGovern, S. L., El Naqa, I., ... & Aviles, M. (2021). Neurocognitive effects and necrosis in childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review. International Journal of Radiation Oncology* Biology* Physics.

69

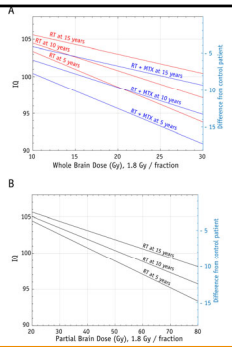
Age as a Risk Factor for RT Late Effects

- Poorest outcomes for youngest patients
- Time since treatment generally negatively correlated with neuropsychological outcomes
- First few years after treatment more noticeable decline; levels off over time
- Patterns of slowed development – younger patients more noticeable decline earlier on
- Patterns of slowed development – older patients may exhibit more protracted decline, less observable in early years post treatment



70

RT Volume, Age, & Combined Treatment Effects



Mahajan, A., Slavnitcha, P. L., Rongthong, W., Brodin, N. P., McGovern, S. L., El Naqa, I., ... & Avanzo, M. (2021). Neurocognitive effects and necrosis in childhood cancer survivors treated with radiation therapy: a PENTEC comprehensive review. International Journal of Radiation Oncology* Biology* Physics.

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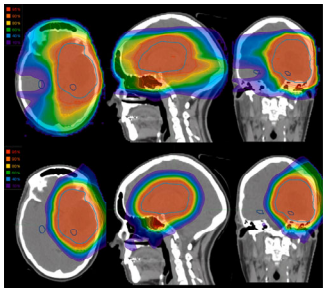
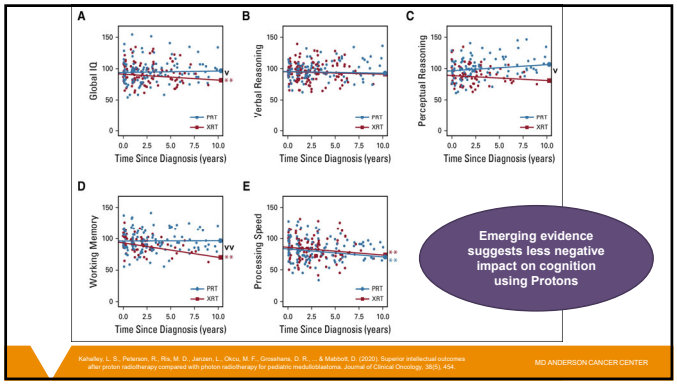
Diagnosis, Treatment, & Patient Experience: Radiation Therapy

Photon vs. Proton



Byskov, C. S., Hansen, C. R., Dahlrot, R. H., Halldbo-Classen, L., Hasslund, C. A., Kjaer-Kristoffersen, F., ... & Kallehauge, J. F. (2021). Treatment plan comparison of proton vs photon radiotherapy for lower-grade gliomas. *Physics and imaging in radiation oncology*, *20*, 98-104.

72


A
B
C
D
E
Global IQ
Verbal Reasoning
Perceptual Reasoning
Working Memory
Processing Speed
PRT
XRT
Time Since Diagnosis (years)
Emerging evidence suggests less negative impact on cognition using Protons
Kahalley, L. S., Peterson, R., Ris, M. D., Janzen, L., Okcu, M. F., Grosshans, D. R., ... & Mabbott, D. (2020). Superior intellectual outcomes after proton radiotherapy compared with photon radiotherapy for pediatric medulloblastoma. Journal of Clinical Oncology, 38(5), 454.
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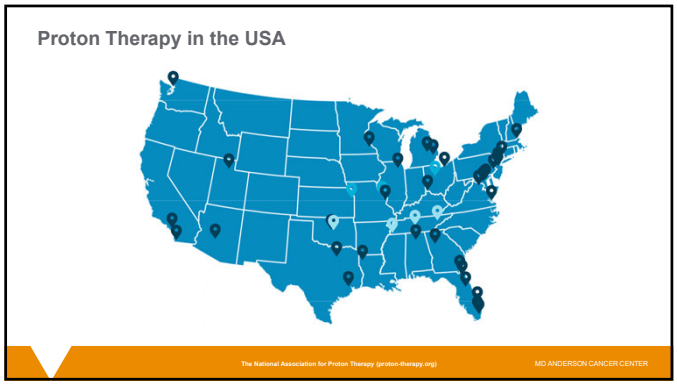
73


Proton Therapy in the USA
The National Association for Proton Therapy (proton-therapy.org)
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Diagnosis, Treatment, & Patient Experience:
Chemotherapy

75

Diagnosis, Treatment, & Patient Experience: Chemotherapy

- Chemotherapy may be standalone treatment or combined with surgery, RT
- Concomitant chemotherapy with radiation appears to confer greater cognitive risk than either treatment in isolation
- Difficult to isolate chemotherapy effects in the context of other treatments, tumor-related variables, and neurological complications

Multiple agents, delivery methods associated with increased risk for cognitive difficulties including:	Risks for sensory impairments such as:
IT Methotrexate (including risk for acute toxicity, persistent leukoencephalopathy)	Platinum based agents: Ototoxicity
High dose Cytarabine	Plant-based alkaloids (e.g., vincristine): Neuropathy

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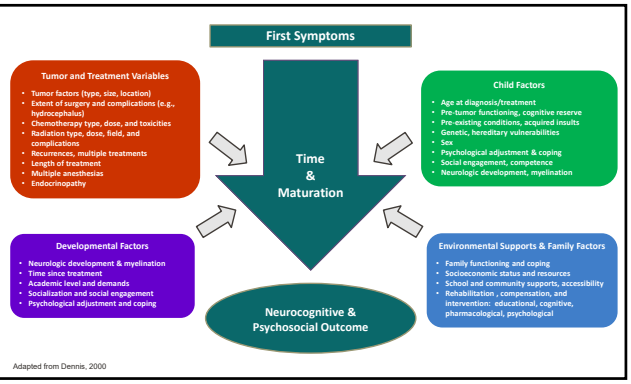
Summary of Factors Related to Expression of Neurocognitive Late Effects

- Tumor size
- Higher risk pathology
- Tumor location
- Neuro complications, esp. hydrocephalus, PFS
- Late neurological complications, e.g., seizures, stroke
- Radiation therapy
- Chemotherapy
- Endocrinopathy
- Sensory deficits
- Tumor recurrence, progression
- Multiple treatments
- Multiple anesthesias
- Younger age at diagnosis/treatment
- Time since treatment
- Premorbid difficulties
- Lower SES (access to resources)
- Higher family stress/conflict
- Sex
- Language
- Genetic polymorphisms

77



Adapted from Dennis, 2000

78

Are pediatric brain tumor survivors at risk for difficulties with:

(Fill in neuropsychological domain here)?

Answer:

YES

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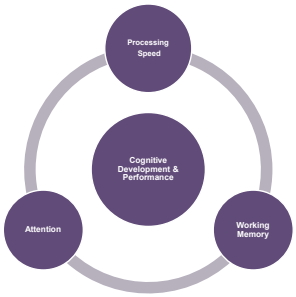
Neuropsychogical phenotypes

Sluggish Cognitive Tempo[1] in PBT Survivors[2]



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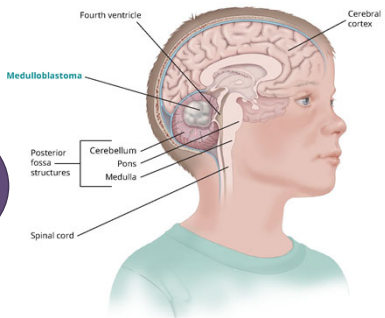
Becker, S. P. (2021). Systematic review: Assessment of sluggish cognitive tempo over the past decade. Journal of the American Academy of Child & Adolescent Psychiatry, 60(6), 690-705.
Penkman, R. A., Jones, A. R., & Jacobson, L. A. (2021). The contribution of sluggish cognitive tempo to processing speed in survivors of pediatric brain tumors. Child Neuropsychology, 27(3), 295-312.

80

Medulloblastoma

Case Examples:

Meg & Jo



https://together.stjude.org/en-us/about-pediatric-cancer/types/brain-spinal-tumors/medulloblastoma.html

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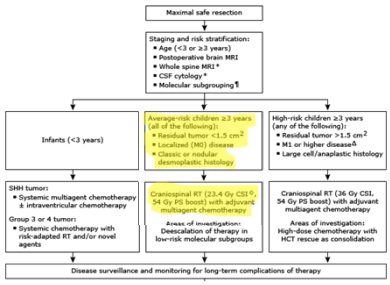
Overview of the treatment of medulloblastoma in children



https://www.uptodate.com/contents/clinical-presentation-diagnosis-and-risk-stratification-of-medulloblastoma

82

Medulloblastoma: Case Examples

Meg (now 15 y.o.)

- MB @ 8 yrs old
- Hydrocephalus, no szs
- Surgery (PFS), Protons, chemo
- GH deficiency
- Sensorineural hearing loss (no ampl)
- Difficulty with balance (ambulates indep)
- Normal vision, uncorrected
- T1: 504; T2: SpEd (OHI)
- Vocal cord compromise (ext. slowed speech)
- No visible distinction

Jo (now 12 y.o.)

- MB @ 4 yrs old
- Hydrocephalus, no szs
- Surgery (no PFS), Photons, chemo
- MTX toxicity
- GH deficiency
- Sensorineural hearing loss (ampl)
- Cataracts
- Persistent ataxia (ambulates with walker)
- T1: SpEd (OHI); T2 SpEd (OHI)
- Slow speech
- Persistent alopecia

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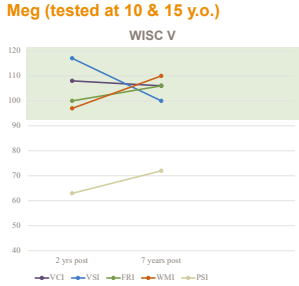
Medulloblastoma

Meg (tested at 10 & 15 y.o.)



Jo (tested at 8 & 12 y.o.)

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Medulloblastoma

	Meg	Jo
Memory	T1 Low average efficiency; good retention, recall T2: Low average efficiency; good retention, recall	T1: Poor efficiency, poor recall, good recognition T2: Poor efficiency, improved recall, good recognition
Motor	Very slow, poor dexterity; low average visual-motor, improved to average at T2	Extremely slow; poor dexterity; extremely low visual-motor; stable over time
EF	Attention normal, slow; stable over time; competent EF performance and ratings, stable over time	T1: Parent rated good; no direct measures T2: Parent rated good; no direct measures
Ratings	T1: no parent concerns (T rates internalizing); socially competent; no SCT T2: Mild internalizing sxs; SCT prominent; decreased socialization; sleep probs	T1: SCT prominent; concerns about future; slow but socially competent T2: SCT prominent; mild internalizing sxs; worry about friendships and self-awareness; sleep probs, sign fatigue

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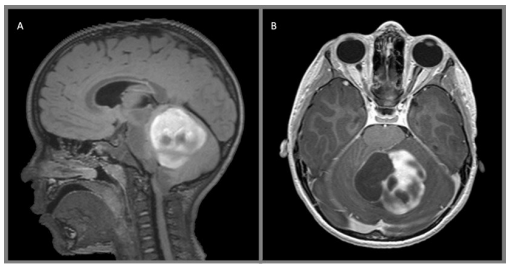
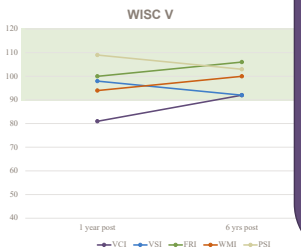
Pilocytic Astrocytoma



https://www.researchgate.net/figure/Juvenile-pilocytic-astrocytoma-WHO-1-A-sagittal-T2-FLAIR-with-contrast-and-B-axial_fig2_341163532

86

Pilocytic Astrocytoma: Beth (now 12 y.o.)

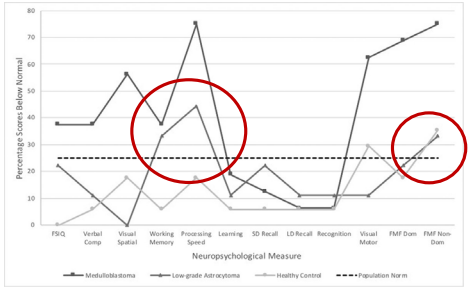


Diagnosed with cerebellar astrocytoma at age 6
Obstructive hydrocephalus; surgery only, no additional complications; tested at 7 and 12 y.o.

- Average reading & math (low average math fluency at T1 & T2)
- Visual motor: T1 = average, T2 below average
- Fine motor: Poor nondominant hand coordination at T1 & T2
- Memory: average efficiency and retention at T1 & T2
- CPT: Normal at T1 & T2
- Language functions: Normal at T1 & T2
- EF: Low avg planning and problem solving at T2
- Shy/reserved; socially competent
- T1: no school support; T2 no school support

87

Comparison of neuropsychological functioning in pediatric posterior fossa tumor survivors: Medulloblastoma, low-grade astrocytoma, and healthy controls



Levitch, C. F., Holland, A. A., Bledsoe, J., Kim, S. Y., Barnett, M., Ramjan, S., & Sands, S. A. (2022). Comparison of neuropsychological functioning in pediatric posterior fossa tumor survivors: Medulloblastoma, low-grade astrocytoma, and healthy controls. Pediatric blood & cancer, 69(2), e29491.

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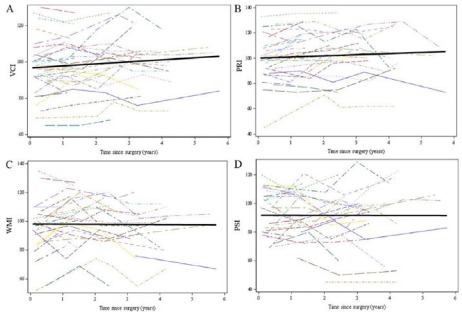
Surgery only low grade glioma – no significant NP change over time



Heitzer, A. M., Raghubar, K., Ris, M. D., Minard, C. G., Gragert, M. N., Stancel, H. H., ... & Kahalley, L. S. (2019). Neuropsychological functioning following surgery for pediatric low-grade glioma: a prospective longitudinal study. Journal of Neurosurgery: Pediatrics, 25(3), 251-259.

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Craniopharyngioma

Neuropsychological Findings*

Largely normal IQ

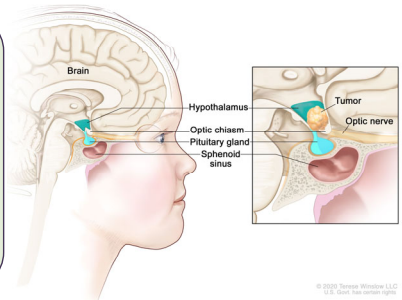
Poor processing speed

Mixed findings for attention

Mixed findings for EF

Memory difficulties common, esp. with hypothalamic involvement

***"results of cognitive testing…may in some cases significantly differ from patients' subjective evaluation or overall functional outcome"** p.19



https://www.cancer.gov/publications/dictionaries/cancer-terms/def/craniopharyngioma

*For review see: Özyurt, J., Müller, H. L., & Thiel, C. M. (2015). A systematic review of cognitive performance in patients with childhood craniopharyngioma. Journal of neuro-oncology, 121(1), 1-21.

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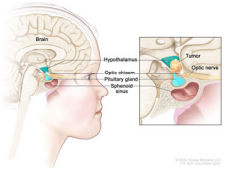
Craniopharyngioma: Amy (now 18)

- Diagnosed with suprasellar craniopharyngioma at age 9
- Treatment included subtotal resection followed by radiation (Photons, IMRT)
- Surveillance shows persistent/stable enlarged ventricles
- Followed by psychiatry for problems with mood, anxiety, impulse control & attention (numerous meds)
- Participating in psychotherapy intermittently
- Meds for hormone replacement and hypertension
- Morbidly obese, poorly regulated eating habits
- Graduating HS successfully with 504 Plan only
  Lots of parental support (not entirely acknowledged)
- Inactivity, sleep problems, fatigue



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Amy (now 18 y.o.)

FSIQ	104
GAI	101
VCI	95
PRI	109
WMI	114
PSI	100

Competent reading, math

Competent language

Competent visual-motor

Competent on direct EF tasks

NP Difficulties

Memory (low efficiency, low recall, poor organization on CVLT)

Self-reported EF difficulties (WM, organization, planning)

Inconsistency on CPT

Observation

Morbidly obese

Poor regulation of eating

Poor time management

Poor emotional regulation

Impulse control a function of interest/engagement (inconsistent motivation)

Seemed to benefit greatly from inherent structure of assessment

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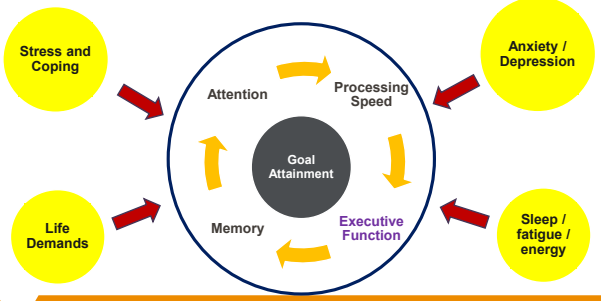
Chain reaction of barriers to success



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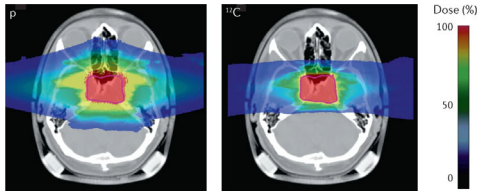
Pediatric Brain Tumors: Future Directions



Emergence of heavy ion therapies may hold promise for even greater sparing of normal tissue

Durante, M., Debus, J., & Loeffler, J. S. (2021). Physics and biomedical challenges of cancer therapy with accelerated heavy ions. Nature Reviews Physics, 3(12), 777-790.

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Pediatric Brain Tumors: Future Directions

Molecularly defined tumor subgroups have both therapeutic and prognostic implications

- Targeted therapies
  - MEK inhibitors
  - BRAF inhibitors
- Immunotherapy
  - Vaccine
  - Adoptive cellular therapies
  - Checkpoint blockade
  - Viral therapies

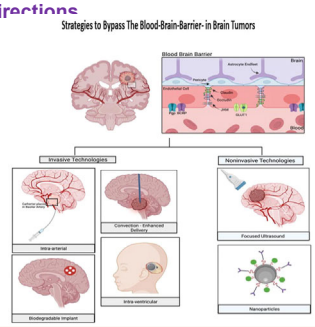

Image from: Power, E. A., Rechberger, J. S., Gupta, S., Schwartz, J. D., Daniels, D. J., & Khatua, S. (2022). Drug Delivery Across the Blood-Brain Barrier for the Treatment of Pediatric Brain Tumors—An Update. Advanced Drug Delivery Reviews, 114303.

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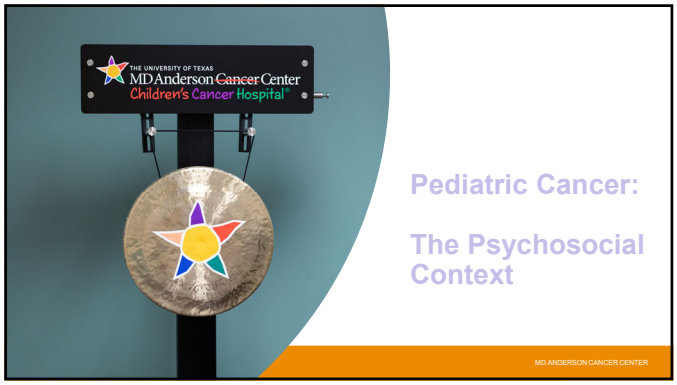

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Psychosocial Context in Pediatric Cancer

- **SES** related to preservation of function (less decline), global cognitive ability, working memory, executive function, school performance processing speed
- **Parental education** related to attention, working memory, school performance, level of cognitive impairment

Sociodemographic & Psychosocial Factors

- **Family functioning** related to processing speed, attention, working memory, verbal memory, executive function
- **Parenting stress** related to school competence, executive function
- **Parenting knowledge/style** associated with cognitive ability
- **Race/ethnicity** findings are somewhat mixed

For review see: Schepers, S. A., Schulte, F. S., Patel, S. K., & Vannatta, K. (2021). Cognitive impairment and family functioning of survivors of pediatric cancer: a systematic review. *Journal of Clinical Oncology*, *39*(14), 1795-1812.

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Psychosocial Context in Pediatric Cancer

Pediatric Blood & Cancer

Supplement Article | Free Access

Standards for the Psychosocial Care of Children With Cancer and Their Families: An Introduction to the Special Issue

Lori Wiener PhD, DCSW, Anne E. Kazak PhD, ABPP, Robert B. Noll PhD, Andrea Farkas Patenaude PhD, Mary Jo Kupst PhD ... See fewer authors

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Psychosocial Standards for Pediatric Oncology

Psychosocial Assessment	Youth with cancer and their family members should routinely receive systematic assessments of their psychosocial health care needs.	Kazak, et al., 2015
Psychosocial Follow-up in survivorship	Long-term survivors of child and adolescent cancers should receive yearly psychosocial screening for adverse educational and/or vocational progress, social and relationship difficulties, distress, anxiety, depression, & risky health behaviors. AYA survivors and their parents should receive anticipatory guidance on the need for life-long follow-up care by the time treatment ends, and repeated at each follow-up visit.	Lown, et al., 2015
Psychosocial Interventions & Therapeutic Support	All youth with cancer and their family members should have access to psychosocial support and interventions throughout the cancer trajectory and access to psychiatry as needed.	Steele, et al., 2015

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Child-directed psychosocial interventions

Residential Camp	Positive feedback, benefit in social skill, self-esteem	Dawson et. Al., 2012; Wu et al., 2010
CBT	Decreased behavior problems, improved social skills, improved attention, reduced internalizing problems	Poggi et al., 2009
Psychoeducational group	Improved self-perceived social competence, positive thinking	Maurice-Stam, et al., 2009
Peer-mediated intervention	Positive impact on peer victimization, rejection; some benefit in number of friend nominations	Devine, et al., 2016
Group social skills intervention	Improved parent and teacher-reported social skills; no significant change in child self-report of social skills/functioning	Schulte, Bartels & Barerra, 2014
Group social skills intervention	Improved parent-reported self-control, social skills	Barerra & Schulte, 2009
Physical activity with psychoeducation & CBT	Little change overall; some long term QoL benefit per parent rating, not self-report	van Dijk-Lokkart et al., 2015

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Psychosocial Standards for Pediatric Oncology

Providing Children & Adolescents Opportunities for Social Interaction	Children & adolescents should be provided opportunities for social interaction during therapy and into survivorship.	Christiansen, et al., 2015
Supporting Siblings	Siblings of children with cancer are a psychosocially at-risk group and should be provided with appropriate supportive services. Parents and professionals should be advised about ways to anticipate and meet siblings' needs, especially when siblings are unable to visit the hospital regularly	Gerhardt, et al., 2015
Psychosocial Care for Parents	Parents & caregivers of children with cancer should have early & ongoing assessment of mental health needs. Access to appropriate interventions for parents and caregivers should be facilitated to optimize parent, child, & family well being.	Kearney et al., 2015

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Psychosocial Interventions Targeting Parents (RCTs)

CBT/Problem Solving Skills Training (Bright Ideas): enhanced problem solving skills, improved mood, decreased posttraumatic stress; durable effect; (Askins et al., 2009; Phipps et al., 2020; Sahler et al., 2002; Sahler et al., 2005; Sahler et al, 2013)

Parent Social Cognitive-Behavioral Intervention Program (P-SCIP); reduced anxiety and PTSS symptoms in parents reduced durable effect (Kazak et al., 2005; Manne et al.2016); Note RCT with parents/patients also improved patient anxiety/arousal (Kazak et al., 2004)

Promoting Resilience in Stress Management for Parents (PRISM-P): manualized brief intervention targeting stress management, goal setting, cognitive reframing and meaning making; associated with improvement in parent reported outcomes for resilience and benefit finding (Rosenberg et al., 2019)

Animal-Assisted Intervention: significantly decreased parenting stress; Children experienced significant reduction in state anxiety (McCullough et al., 2018)

CBT focused on uncertainty, communication with medical staff, cognitive coping, problem solving, social support and consolidation of all skills (Mullins et al., 2012)

Hospital based solution focused brief therapy: improvement in distress, anxiety, somatic symptoms, depression, and improved hope (Zhang et al., 2018)

For review, see: Echa, I. J., Yusufov, M., Isibor, D. A., & Wolfe, J. (2021). A systematic review and meta-analytic evaluation of psychosocial interventions in parents of children with cancer with an exploratory focus on minority outcomes. Pediatric blood & cancer, 68(12), e29328.

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Assessment of Financial Burden	Assessment of risk for financial hardship should be incorporated at time of diagnosis for all pediatric oncology families. Domains of assessment should include risk factors for financial hardship during therapy including: pre-existing low income or financial hardship, single parent status, distance from treating center, anticipated long/intense treatment protocol, and parental employment status. Targeted referrals, longitudinal reassessment.	Pelletier & Bona, 2015

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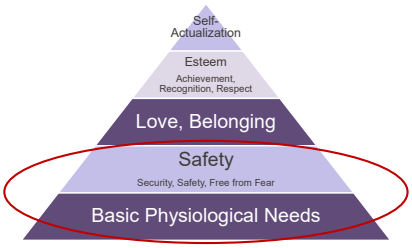

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Neuropsychological Assessment	Children with brain tumors and others at high risk for neuropsychological deficits as a result of cancer treatment should be monitored for neuropsychological deficits during and after treatment.	Annett, Patel, & Phipps, 2015

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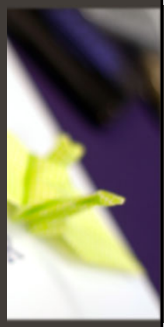
Neuropsychological Outcomes

Clinical Management & Emerging Developments



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COG Long Term Survivorship Guidelines

CHEMOTHERAPY — **ANTIMETABOLITES (CONT)**

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
30	**Antimetabolites** Methotrexate (high dose IV) Methotrexate IO Methotrexate IT	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration - Fine motor dexterity Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change	**HISTORY** **Educational and/or vocational progress** Yearly **SCREENING** **Referral for formal neuropsychological evaluation** Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**HEALTH LINKS** **Educational Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Referral to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Referral to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

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COG Long Term Survivorship Guidelines

RADIATION — **POTENTIAL IMPACT TO BRAIN/CRANIUM (CONT)**

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
46	**Head/Brain** **TBI**	**Neurocognitive deficits** Functional deficits in: - Executive function (planning and organization) - Sustained attention - Memory (particularly visual, sequencing, temporal memory) - Processing speed - Visual-motor integration - Fine motor dexterity - Language - Academic fluency Learning deficits in math and reading (particularly reading comprehension) Diminished IQ Behavioral change	**HISTORY** **Educational and/or vocational progress** Yearly **SCREENING** **Referral for formal neuropsychological evaluation** Baseline at entry into long-term follow-up, then periodically as clinically indicated for patients with evidence of impaired educational or vocational progress	**HEALTH LINKS** **Educational Issues** **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Referral to school liaison in community or cancer center (psychologist, social worker, school counselor) to facilitate acquisition of educational resources and/or social skills training. Psychotropic medication (e.g., stimulants) or evidence-based rehabilitation training. Caution—lower starting dose and assessment of increased sensitivity when initiating therapy is recommended. Referral to community services for vocational rehabilitation or for services for developmentally disabled. **SYSTEM = CNS** **SCORE = 1**

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Psychosocial Standard – Neuropsychological Assessment

TABLE 1. Summary of Evidence Table—Neuropsychological Assessment

Standard	Evidence summary[1]	Methodology[2]	Quality of evidence[3]	Strength of recommendation[4]
Children with brain tumors and others at high risk for neuropsychological deficits as a result of cancer treatment should be monitored for neuropsychological deficits during and after treatment	Empirical research for brain tumors indicates significant impairments associated with tumor and treatment	Cross-sectional; longitudinal studies; significant replication of findings	High	Strong recommendation, given the impact of disease and treatment factors on later neuropsychological functioning
	Evidence gaps: prospective research still needed to assess long-term neuropsychological deficits with other malignancies	Large scale follow-up studies; clinical trials group consensus	Quality of evidence given consistent findings from numerous well-designed studies	

[1]Based on summary of evidence table for that standard; [2]Types of studies: e.g., RCT, cross-sectional, longitudinal; consensus; systematic review articles; [3]Quality of evidence: high = A, moderate = B, low and very low = C (based on GRADE criteria); [4]Strength of recommendation: strong = 1, weak = 2 (based on GRADE quality criteria).

Annett et al., 2015

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TABLE 1 Proposed definitions for levels of neuropsychological care in pediatric oncology

Neuropsychological service	Tools	Provider(s)	Information used for	Referral questions to be answered
Clinical surveillance	Interview, external data, questionnaires	Physician, medical team members	Referral for formal testing or other assessment/intervention as needed	• Perceived cognitive or academic problems?
Consultation	Clinical acumen and review of records, as available	Neuropsychologist	Psychoeducation/guidance; follow-up or prior recommendations; referral for formal testing as needed	• Appropriate for evaluation? • Treatment appropriate based on existing results?
Screening assessment	Interview, questionnaires, neurobehavioral exam, brief test battery	Neuropsychologist with/without technician, and trained medical team members	Referral for formal testing or other assessment/intervention as needed	• Objective cognitive impairment? • Psychosocial concerns?
Targeted neuropsychological evaluation	Test batteries that briefly assess multiple or specific domains focusing on common deficits, interviews, rating scales	Neuropsychologist with/without technician	Treatment planning; future comparisons; referral for comprehensive evaluation as needed	• Can patient make medical decisions/participate in care? • Need education plan? • Tolerate high-risk treatment? • Diagnosis of anxiety, depression, learning disability, or ADHD?
Comprehensive neuropsychological evaluation	Full range of tests and multiple rater questionnaires	Neuropsychologist with/without technician	Differential diagnosis and treatment planning; referral for follow-up as needed	Same questions from targeted evaluation with more data to guide: • Parent/patient/provider education • Treatment planning • Differential diagnosis
Follow-up neuropsychological monitoring	Interview, external data, questionnaires, neurobehavioral exam, brief test battery	Neuropsychologist in collaboration with medical team members	Tracking of neuropsychological trajectory; referral for consultation, formal testing, or other assessment/intervention as needed	• Change in concerns over time? • Objective cognitive impairment? • Psychosocial concerns?

ADHD, attention-deficit hyperactivity disorder.

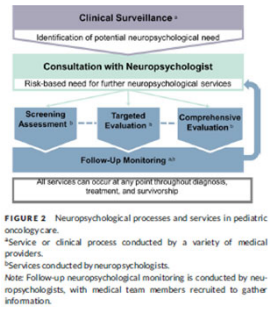

FIGURE 2 Neuropsychological processes and services in pediatric oncology care.
[a]Service or clinical process conducted by a variety of medical providers.
[b]Services conducted by neuropsychologists.
Note: Follow-up neuropsychological monitoring is conducted by neuropsychologists, with medical team members recruited to gather information.

Baum et al., 2017; see also Jacola et al. 2021

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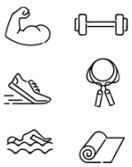

Intervention

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Pharmacologic

Methylphenidate (MPH)

Best evidence from a large, multisite, multiphase trial

- 3 week, randomized, double-blind, placebo-controlled crossover phase
  - Significant improvement in attention for low and moderate MPH doses (parent and teacher ratings) and social skills benefits (teacher ratings).
  - Teacher ratings conservatively reflected a 54% response rate, which is lower than that in ADHD samples (~75%).
- Year-long maintenance phase
  - Benefits in attention (NP measures, parent/teacher/self-report ratings).
  - Academic achievement unchanged, but parent report of improved planning and assignment completion
- Tolerated well, with similar side effects to those in healthy children – highest with CNS tumor, female gender, and low IQ. Deceleration of BMI and weight but not height.
- Utility is limited by medical contraindications and high (36%) parental refusal rate

Conklin et al., 2007, 2009, 2010a, 2010b; Jasper et al., 2009; Mulhern et al., 2004; Nelson et al., 2011

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Pharmacologic

Donepezil

- Adults who received CRT for brain tumor in an open-label phase-II study (n=24; Shaw et al. 2006) and a randomized, placebo-controlled phase III trial (n=198; Rapp et al. 2015)
  - Multiple areas of cognitive improvement (attention & memory) relative to baseline at the end of 24 week trials
  - RCT showed that cognitive improvements were only significant for patients with more significant cognitive impairment at baseline
- Single institution, open-label pilot study in PBT survivors >1yr post-CRT (Castellino et al., 2012)
  - Improvement on measures of executive function and memory (DKEFS Tower, WRAML Visual Memory and Number Letter)
  - Tolerability, some GI concerns without weight loss

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Pharmacologic

Modafinil
Metformin
Prevention?

Modafinil (Provigil)

- Dopaminergic CNS stimulant developed to treat narcolepsy
- Some RCT evidence of improved attention, psychomotor speed, and memory in adult survivors, but benefit not across all studies
- Pediatric brain tumor study ongoing, results pending

Metformin

- Hypoglycemic agent associated with improved declarative and working memory in pediatric brain tumor pilot clinical trial (Ayoub et al., 2020)

Prevention (targeting vascular-based RT injury)

- Memantine (NMDA receptor antagonist used to treat vascular dementia) has been trialed in adults receiving CRT to prevent cognitive dysfunction with mixed results
- 2 preventative Memantine trials underway in PBT

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Cognitive Remediation

In Person, Therapist-Delivered

Cognitive Remediation Program
(Butler & Copeland, 2002)

- Multi-site randomized, clinical intervention trial (n=161, pediatric cancer patients with CNS disease or tx, >1 year off tx, attention deficits per CPT and Conner's ratings) (Butler et al., 2008)
  - **Primary measures:** academic achievement, brief focused attention, working memory, memory recall, vigilance
  - **Secondary measures:** learning strategies, parent/teacher attention ratings, self-esteem self-report
- An fMRI study revealed improved brain activation at tx completion and 6m follow-up in ventral visual areas, cerebellum, SMA, and left frontal cortices that were all diminished at baseline (Zou et al., 2012)

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Cognitive Remediation

Computerized

Cogmed

- 5 to 9 week program (www.cogmed.com)
- Studies in childhood ALL and pediatric brain tumor samples have demonstrated feasibility and acceptability (Cox et al. 2015; Hardy et al. 2013)
- Single-blind, waitlist-controlled trial in ALL and pediatric brain tumor who received CNS-directed therapy
  - Improvement in targeted skills (working memory, attention, and processing speed) as per performance-based measures and caregiver ratings that are maintained up to 6 months
  - Poor generalization to functional academic improvements
  - fMRI findings of training-related neuroplasticity in left prefrontal, bilateral medial frontal, and left cingulate areas that were not associated with working memory scores

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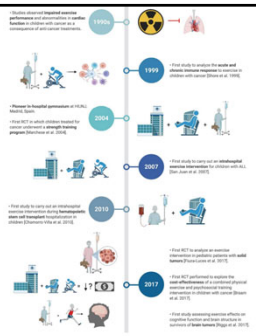
Cognitive Remediation

Physical Activity



Morales et al., 2021

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Physical Activity

- Physical activity has been shown to facilitate neuroplasticity and hippocampal neurogenesis in both humans and nonhumans (Winocaur et al., 2014; Wong-Goodrich et al., 2010), increase growth hormone, and reduce inflammation (Blackmore et al., 2009, Handschin & Speigelman, 2008, Hotting & Roter, 2013)
- Pediatric Brain Tumor
  - Exercise training is acceptable and feasible
  - Positive impact on processing speed and attention control, but review of 5 RCTs indicates effect of exercise on cognition is not clear
  - The best effect was shown in studies that included social interaction/group exercise

(Riggs et al., 2017; Szulc-Lerch et al., 2018; Cox et al., 2020)

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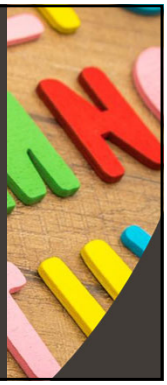
Educational Outcomes



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Psychosocial Standards for Pediatric Oncology

Academic Continuity & School Reentry Support	In collaboration with parents, school-aged youth diagnosed with cancer should receive school reentry support that focuses on providing information to school personnel about the patient's diagnosis, treatment, and implications for the school environment and provides recommendations to support the child's school experience. Pediatric oncology programs should identify a team member with the requisite knowledge and skills who will coordinate communication between the patient/family, school, and the health care team.	Thompson, et al., 2015

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Educational Outcomes after Pediatric Cancer

- More likely to receive special education support
- More likely to repeat a grade
- Increased likelihood of delays in completing education
- More likely to attend non-mainstream education
- Lower academic achievement in general, less likely to have college degree

Increased risk for unemployment

Increased risk for lower income

Additional adverse health outcomes related to financial burden

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Educational Outcomes after Pediatric Brain Tumor

- More likely to fail, repeat a grade
- Perform more poorly than peers on standardized tests
- Require more educational support than other pediatric cancer survivors
- Lowest educational attainment among cancer survivors
- Lower incomes, higher unemployment rates compared to other pediatric cancer survivors
- Increased risk for dependence on others into adulthood

For review, see: Stavinoha, P. L., Trinh-Wong, T., Rodriguez, L. N., Stewart, C. M., & Frost, K. (2021). Educational Pain Points for Pediatric Brain Tumor Survivors: Review of Risks and Remedies. Children, 8(12), 1125.

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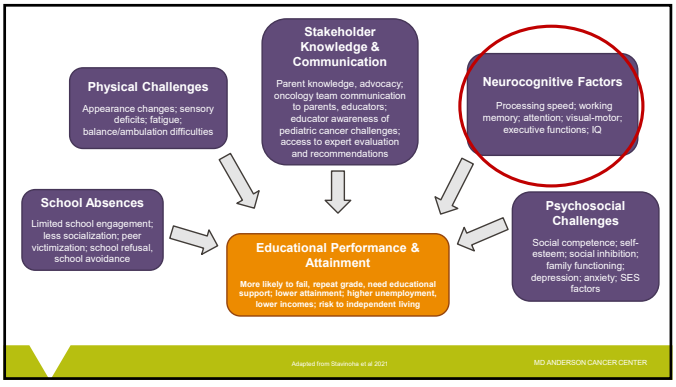

Adapted from Stavinoha et al 2021

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Current State of Educational Supports

Hospital-based interventions

Instructional continuity, clinic-based intervention

Home-based interventions

Cognitive remediation, parent coaching

School Liaison Program

Improved access to services; improved parent advocacy; improved educator confidence

Accommodations & Special Education Services

Access to support services in public school

For review, see: Marchak, J. G., Devine, K. A., Hudson, M. M., Jacobson, L. A., Michel, G., Peterson, S. R., ... & Sands, S. A. (2021). Systematic review of educational supports of pediatric cancer survivors. Current approaches and future directions. Journal of clinical oncology: official journal of the American Society of Clinical Oncology, JCO2002471.

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Hospital School-Liaison and Re-Entry Programs

- **Facilitate communication between family, medical team, and educators**
- **Educate parents and educators (improved parent advocacy, educator knowledge & confidence)**
- **Improved peer knowledge and attitude toward pediatric cancer survivor**
- **Improved academic achievement and social adjustment of survivors**
- **Usually not reimbursable services and limited availability**

HEAL
THE HOSPITAL EDUCATOR AND ACADEMIC LIAISON ASSOCIATION

For review, see: Stavinoha, P. L., Trinh-Wong, T., Rodriguez, L. N., Stewart, C. M., & Frost, K. (2021). Educational Pain Points for Pediatric Brain Tumor Survivors' Review of Risks and Remedies. Children, 8(12), 1125.

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TABLE 2. Surveillance Recommendations for Education in Survivors of CAYA Cancers

Who Needs Surveillance?

Health care providers, teachers, caregivers, survivors of CAYA cancers, and survivors' schools should be aware that, on a group level, survivors of CAYA cancer are at risk for
Lower educational achievement (Level C evidence).
Experiencing a delay in completing their education (Level A evidence).
Requiring educational accommodations (Level B evidence).
Particular attention is needed for survivors of CAYA cancer with the following risk factors[a] for lower educational achievement: primary diagnosis of a CNS tumor (Level B evidence), CNS-directed therapies (concordant in existing guidelines, expert opinion), impaired neurocognitive functioning (Level A evidence), non-White race or immigration status (Level A evidence for specific geographical regions), and parents' lower level of education (Level B).

At What Age or Time From Exposure Should Surveillance Be Initiated?

Surveillance of educational outcomes is recommended for all ages to begin at diagnosis and continue through survivorship until young adulthood (expert opinion).

What Surveillance Modality Should Be Used and at What Frequency Should Surveillance Be Performed?

Regular assessment of educational outcomes[a] via parent report or self-report is recommended at every long-term follow-up visit or general medical checkup at least annually[b] until education is completed (expert opinion).

What Should Be Done If Abnormalities Are Identified?

Documentation of educational problems in the survivor's medical record is recommended to facilitate sharing with all members of the care team (expert opinion).
Referral[a] to an educational specialist, psychologist, and/or social worker for assessment and implementation of relevant educational and/or disability services is recommended for survivors who report educational problems upon screening (expert opinion).

A. Ohrstein, S. Mulder, R. L. Brown, M. Ch. Ingerski, L. M. Mader, ... & International Late Effects of Childhood Cancer Guideline Harmonization Group. Survivor A report from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Survivor

TABLE 3. Surveillance Recommendations for Employment in Survivors of CAYA Cancers

Who Needs Surveillance?

Health care providers, caregivers, and survivors of CAYA cancers should be aware that, on a group level, survivors of CAYA cancer are at risk for unemployment (Level B evidence).
Particular attention is needed for survivors of CAYA cancer with the following risk factors[a] for unemployment: female sex (Level B evidence), lower educational achievement (Level A evidence), primary diagnosis of a CNS tumor (concordant in existing guidelines, Level A evidence), CNS-directed therapies (concordant in existing guidelines, Level A evidence), any adverse long-term side effects (Level A evidence), impaired neurocognitive functioning (Level A evidence), second malignancy or recurrence (Level B evidence), psychological distress (Level B evidence), and physical disability (Level B evidence).

At What Age or Time From Exposure Should Surveillance Be Initiated?

Vocational planning and employment surveillance are recommended to begin in adolescence to support survivors to transition from education to employment (expert opinion).

What Surveillance Modality Should Be Used and at What Frequency Should Surveillance Be Performed?

Regular assessment of vocational planning[a] and employment status via parent report or self-report is recommended at every long-term follow-up visit or general medical checkup (expert opinion).

What Should Be Done if Abnormalities Are Identified?

Documentation of vocational problems in the survivor's medical record is recommended to facilitate information sharing with all members of the care team (expert opinion).
[a] to a vocational counselor, psychologist, and/or social worker assessment and implementation of relevant vocational and/or disability services is recommended for survivors who report vocational problems upon screening (expert opinion).

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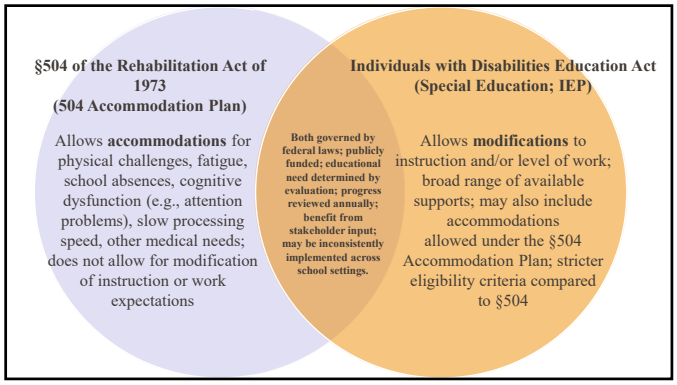
§504 of the Rehabilitation Act of 1973
(504 Accommodation Plan)
Allows accommodations for physical challenges, fatigue, school absences, cognitive dysfunction (e.g., attention problems), slow processing speed, other medical needs; does not allow for modification of instruction or work expectations
Both governed by federal laws; publicly funded; educational need determined by evaluation; progress reviewed annually; benefit from stakeholder input; may be inconsistently implemented across school settings.
Individuals with Disabilities Education Act (Special Education; IEP)
Allows modifications to instruction and/or level of work; broad range of available supports; may also include accommodations allowed under the §504 Accommodation Plan; stricter eligibility criteria compared to §504

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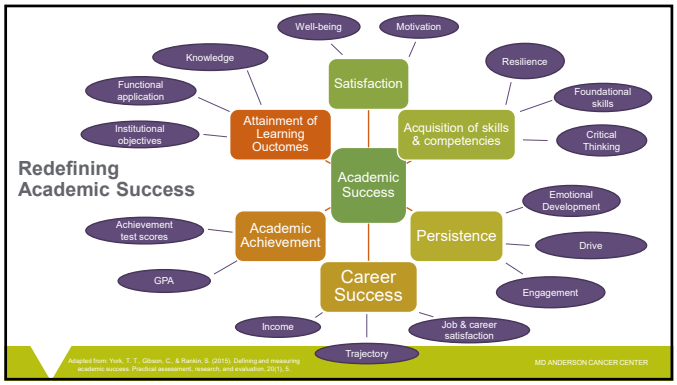
Redefining Academic Success
Well-being
Motivation
Knowledge
Resilience
Functional application
Satisfaction
Foundational skills
Attainment of Learning Outcomes
Acquisition of skills & competencies
Institutional objectives
Critical Thinking
Academic Success
Emotional Development
Achievement test scores
Academic Achievement
Persistence
Drive
GPA
Career Success
Engagement
Income
Job & career satisfaction
Trajectory
Adapted from: York, T. T., Gibson, C., & Rankin, S. (2015). Defining and measuring academic success. Practical assessment, research, and evaluation, 20(1), 5.
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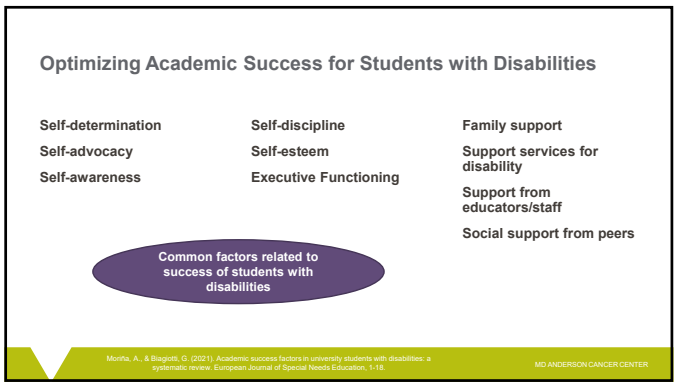
Optimizing Academic Success for Students with Disabilities
Self-determination
Self-advocacy
Self-awareness
Self-discipline
Self-esteem
Executive Functioning
Family support
Support services for disability
Support from educators/staff
Social support from peers
Common factors related to success of students with disabilities
Moriña, A., & Biagiotti, G. (2021). Academic success factors in university students with disabilities: a systematic review. European Journal of Special Needs Education, 1-18.
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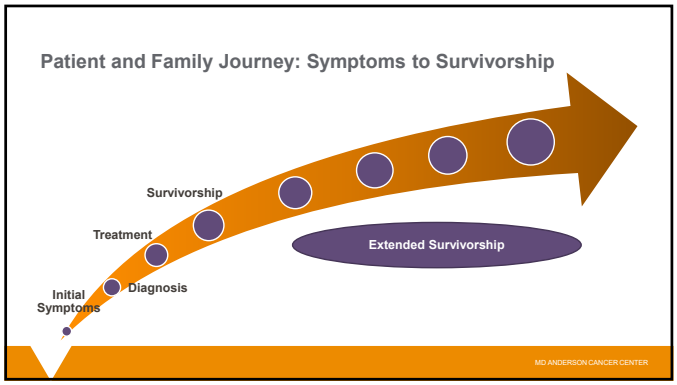

131

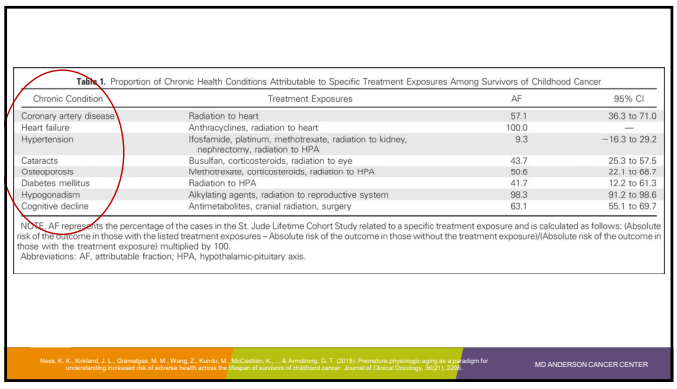

Table 1. Proportion of Chronic Health Conditions Attributable to Specific Treatment Exposures Among Survivors of Childhood Cancer

Chronic Condition	Treatment Exposures	AF	95% CI
Coronary artery disease	Radiation to heart	57.1	36.3 to 71.0
Heart failure	Anthracyclines, radiation to heart	100.0	—
Hypertension	Ifosfamide, platinum, methotrexate, radiation to kidney, nephrectomy, radiation to HPA	9.3	−16.3 to 29.2
Cataracts	Busulfan, corticosteroids, radiation to eye	43.7	25.3 to 57.5
Osteoporosis	Methotrexate, corticosteroids, radiation to HPA	50.6	22.1 to 68.7
Diabetes mellitus	Radiation to HPA	41.7	12.2 to 61.3
Hypogonadism	Alkylating agents, radiation to reproductive system	98.3	91.2 to 98.6
Cognitive decline	Antimetabolites, cranial radiation, surgery	63.1	55.1 to 69.7

NOTE. AF represents the percentage of the cases in the St. Jude Lifetime Cohort Study related to a specific treatment exposure and is calculated as follows: (Absolute risk of the outcome in those with the listed treatment exposures − Absolute risk of the outcome in those without the treatment exposure)/(Absolute risk of the outcome in those with the treatment exposure) multiplied by 100.
Abbreviations: AF, attributable fraction; HPA, hypothalamic-pituitary axis.

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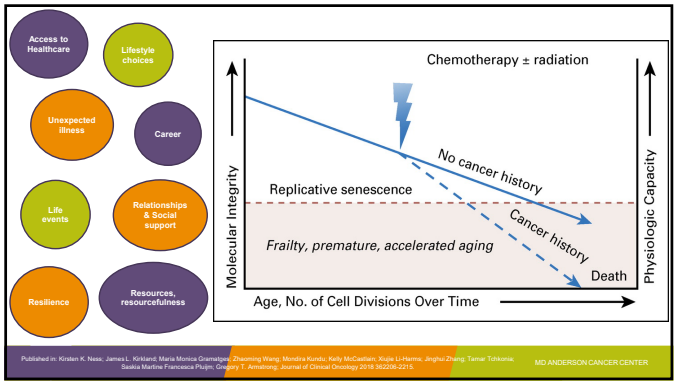
Access to Healthcare
Lifestyle choices
Unexpected illness
Career
Life events
Relationships & Social support
Resilience
Resources, resourcefulness
Chemotherapy ± radiation
No cancer history
Replicative senescence
Cancer history
Frailty, premature, accelerated aging
Death
Molecular Integrity
Physiologic Capacity
Age, No. of Cell Divisions Over Time
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Resources
CANCERcare
Children's Brain Tumor Foundation
American Cancer Society
NIH NATIONAL CANCER INSTITUTE
CHILDREN'S ONCOLOGY GROUP
CURESEARCH FOR CHILDREN'S CANCER
LEUKEMIA & LYMPHOMA SOCIETY
HEAL
The National Children's Cancer Society
ALONG COMES HOPE
Mattie Miracle CANCER FOUNDATION
Cancer.Net
ASCO | KNOWLEDGE CONQUERS CANCER
The Childhood Brain Tumor Foundation
Pediatric Brain Tumor Foundation
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