TSH ANNUAL MEETING#59
"HEMATOLOGY IN TIMES OF PRECISION & INNOVATION"
6-9 MARCH, 2022

Minimized Cardiologic and Neurologic Toxicities

Supportive care in pediatric acute leukemia

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Pediatric Cancer & Hematologic Disorde
PedHemOnc-PMK

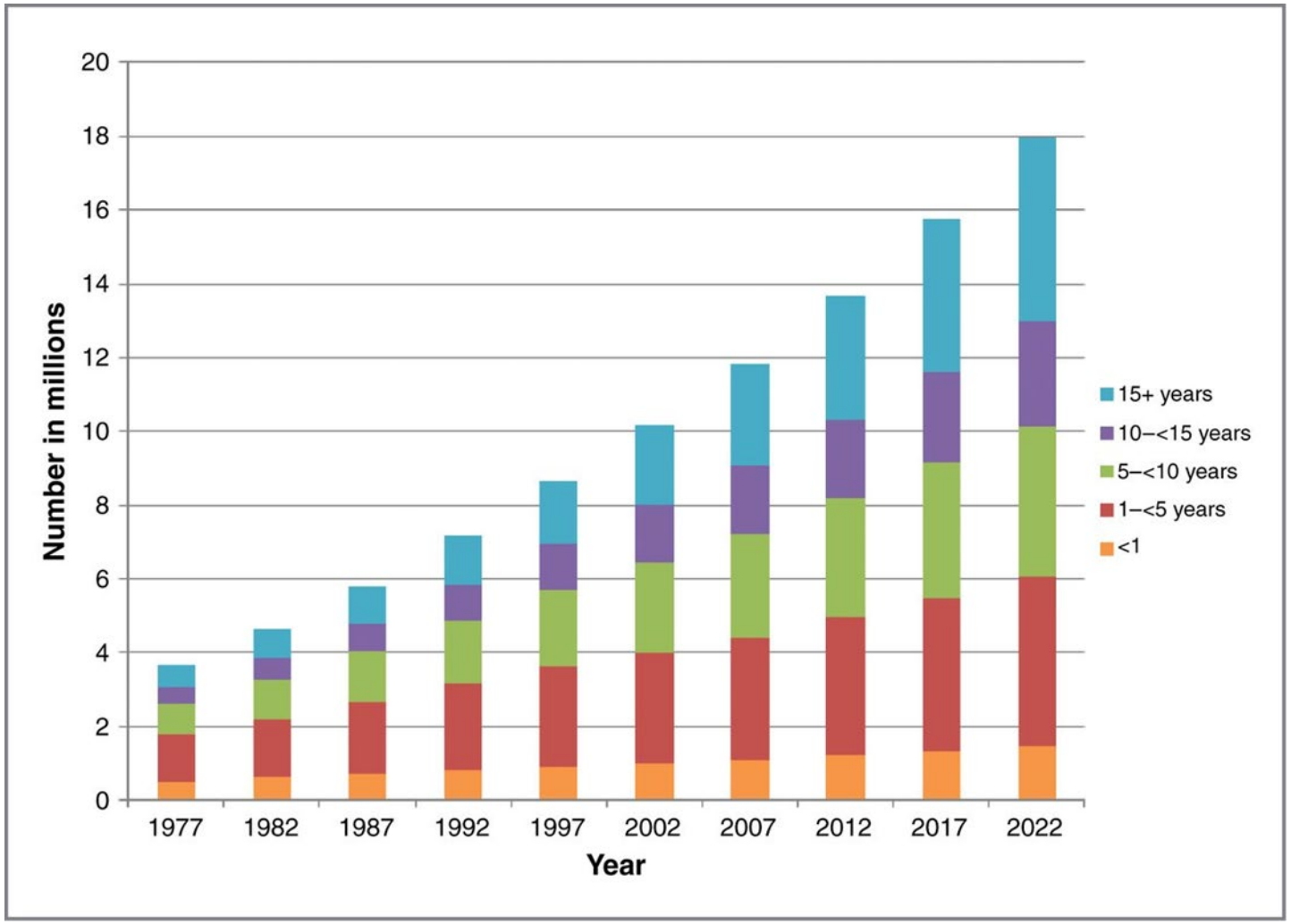
PED PMK

CANCER SURVIVOR CLINIC

Outlines

- Introduction
- Cardiologic and neurologic toxicities
  - Acute toxicities
  - Late toxicities
- Late/long term side effects
  - Cardiologic and neurologic
  - Treatment and prevention

Estimated and projected number of cancer survivors in the United States from 1977 to 2022 by years since diagnosis.



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Janet S. de Moor et al. Cancer Epidemiol Biomarkers Prev 2013;22:561-570

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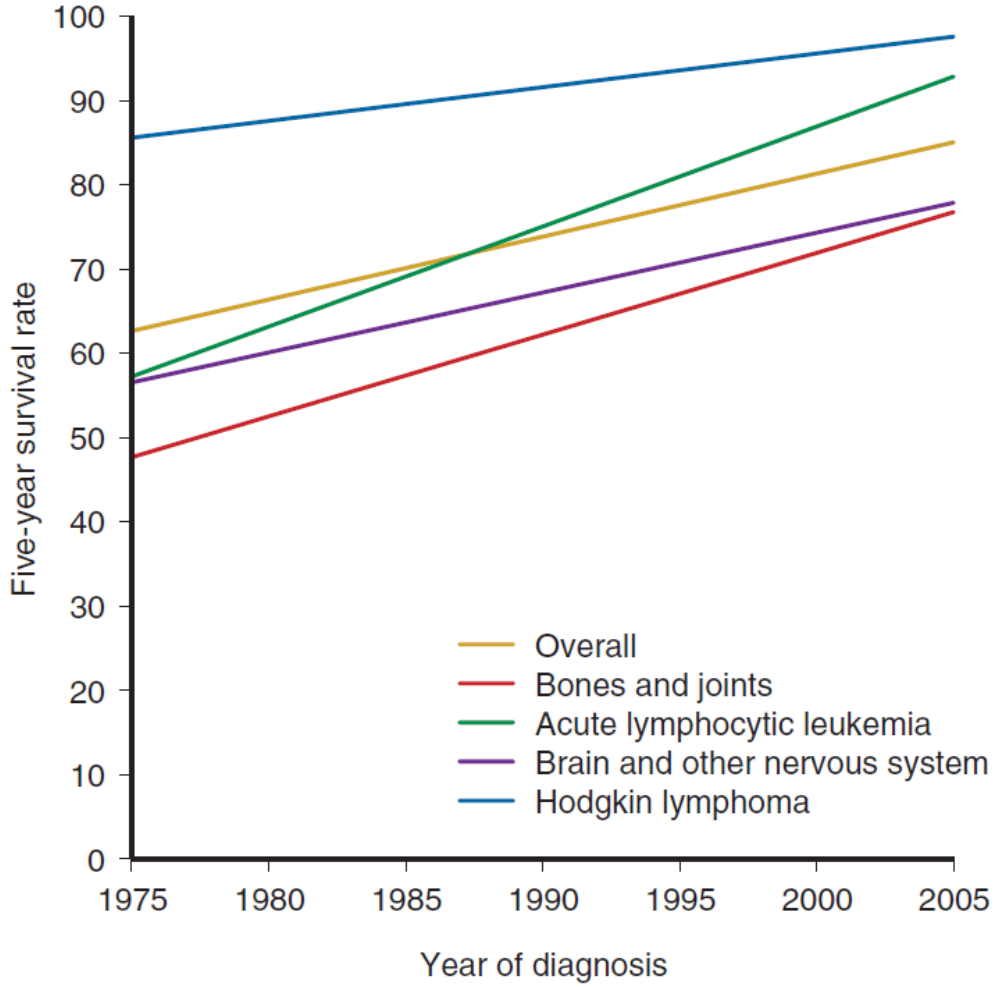
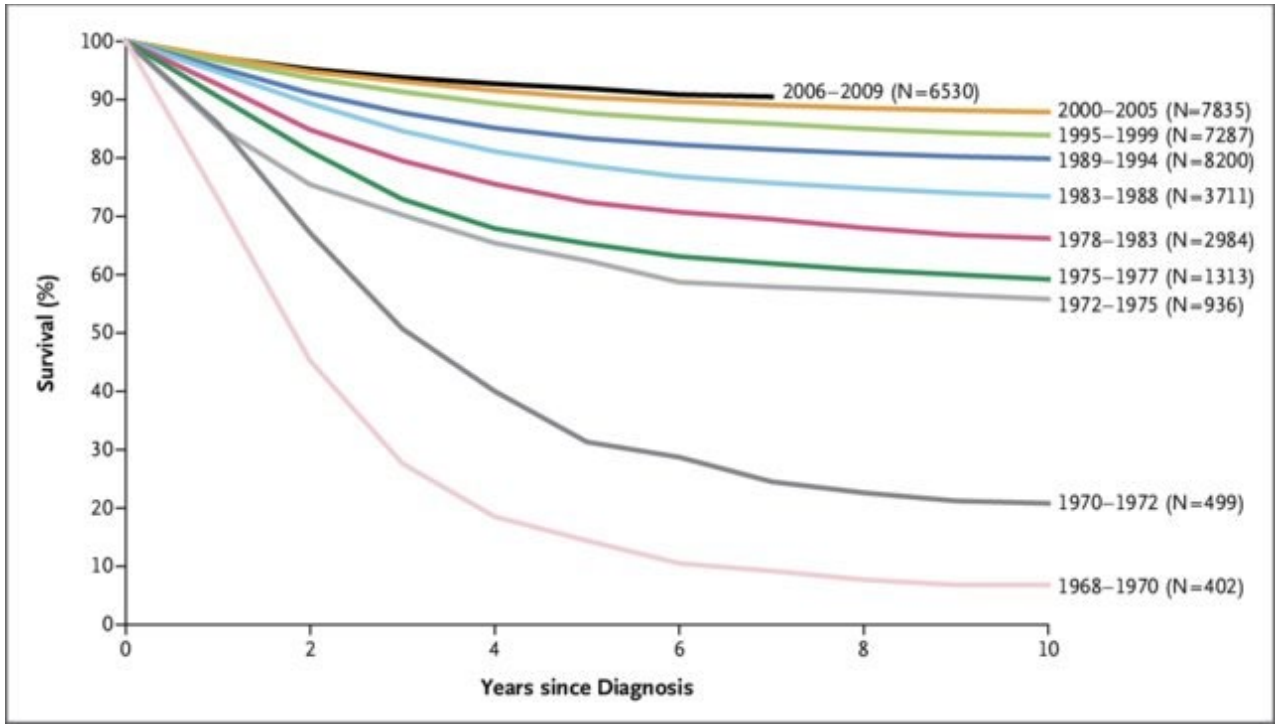
5-year Cancer Survival, Age < 20 years



Modified from: Howlader N, Noone AM, Krapcho M, et al, editors: SEER cancer statistics review, 1975-2010. Bethesda, Maryland, National Cancer Institute.

Overall Survival among Children with ALL



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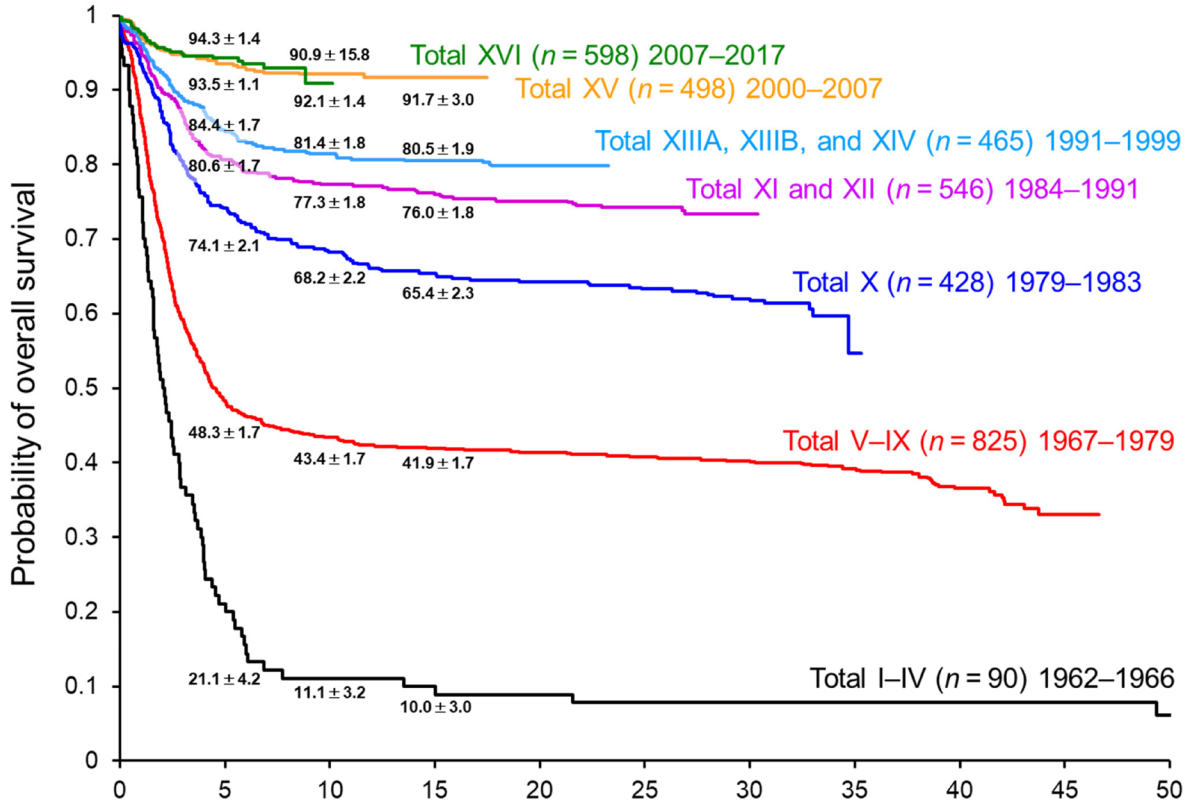

SJCRH

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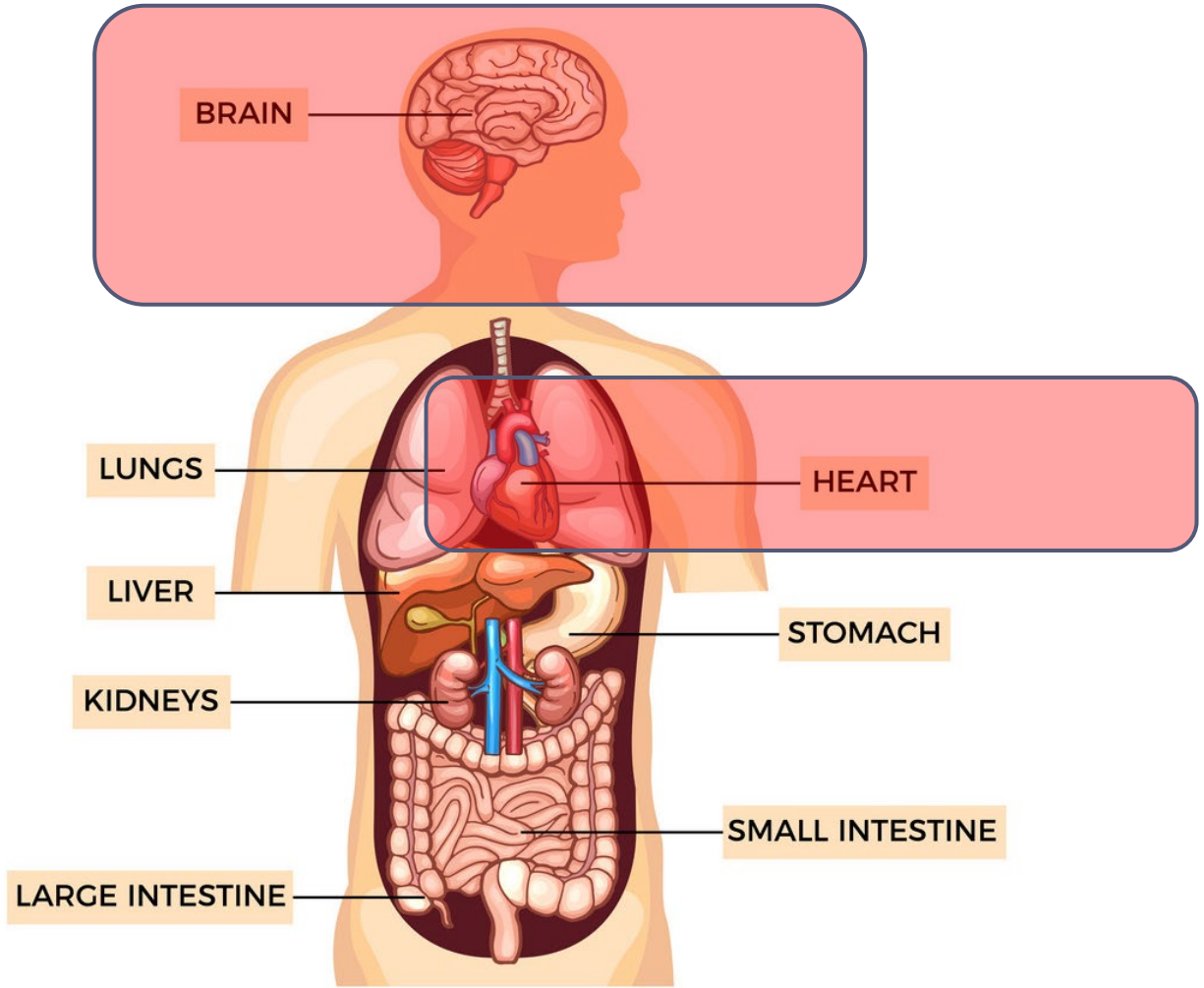
Hunger SP, Mullighan CG. NEJM. 2015;373(16):1541-52.
Inaba H, Pui C-H. Journal of Clinical Medicine. 2021; 10(9):1926.

Acute vs. Late Toxic effects for Childhood leukemia



https://www.baamboozle.com/game/27654

THE LANCET
Oncology

REVIEW | VOLUME 17, ISSUE 6, E231-E239, JUNE 01, 2016

Consensus definitions of 14 severe acute toxic effects for childhood lymphoblastic leukaemia treatment: a Delphi consensus

Prof Kjeld Schmiegelow, MD • Andishe Attarbaschi, MD • Shlomit Barzilai, MD • Gabriele Escherich, MD • Thomas Leth Frandsen, MD • Christina Halsey, MD • et al. Show all authors • Show footnotes

Published: June, 2016 • DOI: https://doi.org/10.1016/S1470-2045(16)30035-3 •

Check for updates

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Acute Toxic effects for Childhood ALL

Asparaginase hypersensitivity	
Asparaginase-associated pancreatitis	GI
Sinusoidal obstruction syndrome	
Hyperlipidemia	Endocrine
Osteonecrosis	Bone
Arterial hypertension	CVS

Schmiegelow K, et al. The Lancet Oncology. 2016 Jun 1;17(6):e231-9.

Acute Toxic effects for Childhood ALL

Posterior reversible encephalopathy syndrome (PRES)	Neuro
Seizures	
Depressed level of consciousness	
Methotrexate-related stroke-like syndrome	
Peripheral neuropathy	
High-dose methotrexate-related severe nephrotoxicity	Nephro
Thromboembolism	Hemato
PCP pneumonia	Infection

Schmiegelow K, et al. The Lancet Oncology. 2016 Jun 1;17(6):e231-9.

Arterial Hypertension

- SBP and/or DBP ≥95th percentile for sex, age, and height x 3
  1. SBP or DBP in the 90th–95th percentile for age and/or BP > 120/80 mm Hg
  2. Recurrent or persistent SBP or DBP greater than the 95th percentile for age x3 or lasting >72 h with monotherapy indicated
  3. Recurrent or persistent SBP or DBP >95th percentile for age x3 or lasting >72 h and needing > 1 drug or additional intensive treatment than grade 2 for blood pressure control.
  4. Life-threatening consequences (eg, hypertensive crisis with transient or permanent neurological deficit and urgent intervention needed).
  5. Death from hypertension

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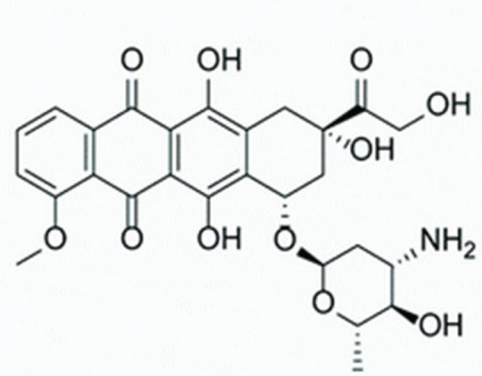
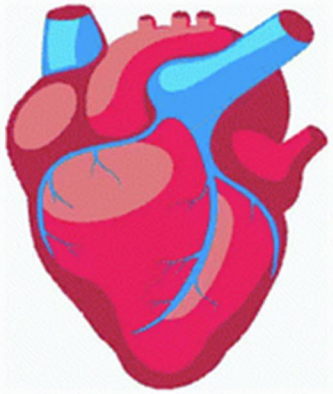
Schmiegelow K, et al. The Lancet Oncology. 2016 Jun 1;17(6):e231-9.

Doxorubicin Induced Cardiotoxicities





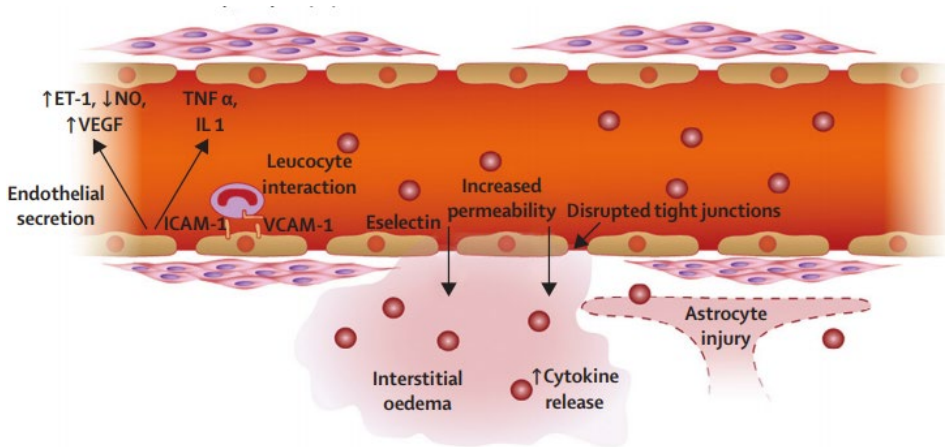
Acute Cardiotoxcicity → Early Stage Chronic Cardiotoxcicity → Late Stage Chronic Cardiotoxcicity

High **Cardiotoxicity Reversibility** Low

Qin Y, Guo T, Wang Z, Zhao Y. Journal of Materials Chemistry B. 2021.

Posterior Reversible Encephalopathy Syndrome

- Disorder of reversible subcortical vasogenic brain edema
- Patients with acute neurological symptoms (eg, seizures, encephalopathy, headache, and visual disturbances)
- The setting of renal failure, blood pressure fluctuations, cytotoxic drugs, autoimmune disorders, and preeclampsia or eclampsia
- Pathophysiological changes underlying PRES are not fully understood, *endothelial dysfunction* is a key factor.



Jennifer E Fugate et al, Lancet Neurol 2015

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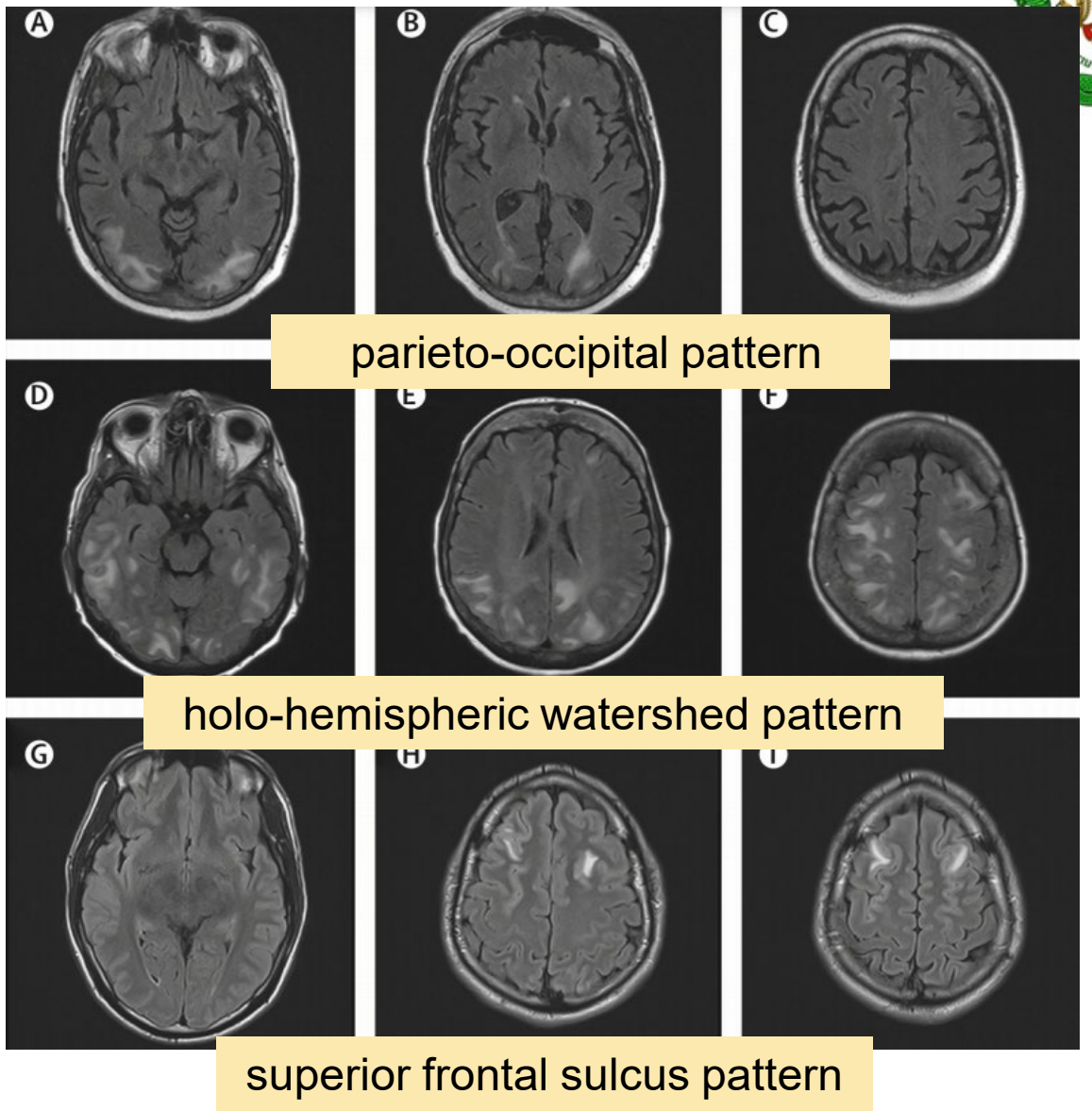
Imaging

- Brain MRI (FLAIR) is much more sensitive
- Vasogenic edema is usually asymmetric, but almost always bilateral
- Three primary area 70%
  1. parieto-occipital pattern
  2. holo-hemispheric watershed pattern
  3. superior frontal sulcus pattern



Courtesy by Piradee Suwanpakdee, MD. (with permission)

Severe, Fatal Methotrexate-related Neurotoxicity in 2 Adolescent Patients With ALL

Sarah Dabagh, MD, Henry David, MD,† Sarah Young, MD,‡ Andrew Doan, MD,§ and Deepa Bhojwani, MD§*

TABLE 1. Pediatric Cases of Persistent Methotrexate Neurotoxicity in the Absence of Radiation

Patient No.	Diagnosis	Age (y)	Sex	Therapy Protocol	Days since IT MTX	Stage of Therapy	Initial Physical Findings	Treatment	Persistent Deficits
1	ALL	17	F	Per COG AALL1131	37	Maintenance cycle 4	Auditory hallucinations, cranial nerve deficits, respiratory distress requiring ventilation	Antimicrobials aminophylline steroids IVIG plasmapheresis rituximab	Quadriplegia, ventilator dependence
2	ALL	20	F	Per COG AALL1131	11	Interim maintenance	Confusion, disinhibition, tingling, slurred speech, ataxia, respiratory distress requiring ventilation	Antimicrobials, dextromethorphan, aminophylline	Encephalopathy
3	ALL	17	M	UKALL2003	6	Consolidation	Disorientation, agitation, dysphasia	Antimicrobials	Deficit in executive functioning (particularly word processing)
4	ALL	14	F	UKALL2003	6	Consolidation	Quadriparesis, aphasia, respiratory distress requiring ventilation	Aminophylline folinic acid	Quadriplegia and dysarthria
5	ALL	17	M	UKALL2003	8	Consolidation	Arm monoparesis, confusion, aphasia	Anticonvulsants Antimicrobials	Persistent impairment in short-term memory and ataxia
6	ALL	7	F	CoALL 08-09	4	Induction	Somnolence, respiratory distress requiring ventilation, impaired speech, and motor function	Antimicrobials antifungals antivirals folinic acid aminophylline	Persistent limitations in cognitive function

Patients 1 and 2 reflect the patients in this series reflecting cases 1 and 2, respectively, and patients 3 to 5 reflect the survey findings from Bond et al[4] in the UKALL 2003 trial, and patient 6 obtained from Löbel et al.[5] Of note, patient 6 received nitrous oxide during her intrathecal methotrexate administration and this was felt by the author to be a possible contributing factor.
ALL indicates acute lymphoblastic leukemia; IVIG, intravenous immunoglobulin.

The risk factors include

- Age > 10 years
- Patients with high-risk ALL
- Higher cumulative number of IT doses
- Higher ratio of 42-hour plasma MTX concentration to leucovorin rescue
- Genetic polymorphisms
- Concurrent radiation

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JPHO 2019

Neurotoxicity from Methotrexate

TABLE 1 | Toxicity associated with the most common chemotherapeutic agents used in pediatric onco-hematology.

Neurologic toxicity	Neuroradiologic features	Risk factors and route of administration	Time of onset and duration	Incidence
Methotrexate				
Acute chemical meningitis	Thickened and gadolinium-enhancing nerve sleeves in case of adhesive arachnoiditis	Intrathecal (i.t.)	Onset within few hours with complete recovery in 2–3 days	5–40%
Transverse myelopathy	Signal hyperintensity of the lateral and dorsal columns in T2-weighted magnetic resonance imaging (MRI), often with contrast enhancement (vacuolar demyelination and necrosis of the spinal cord)	i.t. often associated with i.t. cytarabine in heavily treated patients	Onset within hours or days with only some degree of recovery	Rare
(Sub)acute toxicity with stroke-like symptoms or seizure	Transient restricted diffusion on diffusion-weighted MRI, compatible with cytotoxic edema	i.t. or intravenous (i.v.) (moderate–high doses)	Brief episodes of symptoms few days/weeks after 2–3 courses	3–15%
Subacute leukoencephalopathy (LE)	White matter hyperintensity on T2-weighted and FLAIR MRI	Multiple courses of i.t. and i.v.	Development with repeated courses with variable persistence after the end of therapy	3.8% (symptomatic)–20% (asymptomatic)
Chronic LE	Periventricular white matter hyperintensity with possible temporary focal enhancement, ventriculomegaly and cortical atrophy	Repeated doses of i.t. or i.v. (high doses) but most frequent in combination and/or with brain radiotherapy	Onset several months to years after administration with variable clinical course	2% [i.v. methotrexate (MTX) alone]–45% (MTX + radiotherapy or i.t. MTX)

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Cordelli, et al. Central Nervous System Complications in Children Receiving Chemotherapy or Hematopoietic Stem Cell Transplantation. Pediatric CNS Complications of Chemotherapy/HSCT 105(2017).

Peripheral Neuropathy

Vincristine-induced peripheral neuropathy

Table 1. Objective Peripheral Neuropathy Assessment Approaches for Use in Children [14, 38, 99]

Test	Nerve Fiber Evaluated	Procedure	Advantages	Disadvantages
Deep Tendon Reflexes	Large	Reflexes are graded on a scale from 0 (normal) to 4 (all reflexes absent). Test using a reflex hammer with the child's limbs relaxed. Test bilateral Achilles, patellar, brachioradialis, bicep, and tricep tendon reflexes.	The test can be conducted quickly and with children <5 years of age.	Some children may elicit a "fake" reflex response by moving their leg or ankle on their own. The child may have trouble sitting still and relaxed during the test. Requires clinician training and practice to increase testing accuracy.
Strength	Large	Strength is scored from 0 (normal) to 4 (paralysis). While sitting on an exam table or on the edge of the bed, the child is asked to: • Curl their toes downward and resist clinician attempts to uncurl their toes. • Flex the foot upwards and resist clinician attempts to push the foot down. • Push down on the clinician's hand with their foot as if the hand is a gas/brake pedal, and resist clinician attempts to push the foot up. • Raise the leg (with knee bent) and resist clinician attempts to push the leg down. • Make a fist and resist clinician attempts to bend their wrists while the clinician pushes up and down on the fist. • Grip two of the clinician's fingers with their hands and resist clinician attempts to pull their fingers out of the child's grip. • Flex both arms/biceps and to resist clinician attempts to extend (un-flex) the arms. • Hold both arms out to the side (like wings) and resist clinician attempts to push the arms back down to the child's sides.	The child may enjoy proving his/her strength.	It may be difficult for the clinician to objectively score diminished strength. The test is time-consuming and difficult to conduct in very young children.
Vibration sensation	Large	Strike a 128 Hz tuning fork with the palm of the hand and place the tip to the bony surface of the great toe bilaterally. Ask the child tell when the "buzzing" or "vibration" has stopped. Perform this test bilaterally and move from distal to proximal areas if no vibration is felt.	The test requires minimal clinician training. Children enjoy the testing.	The test requires that children be continually re-focused on the vibration sensation. Young children may not be able to communicate precisely when the vibration stops.
Semmes-Weinstein Monofilaments (Pressure)	Large	Ask the child to close their eyes. Place the smallest filament at different locations on each hand and foot for a couple seconds each time. Ask the child to state when they feel the filament touch their skin. Vary the sites and speed of the test so that the child cannot predict the next location. If the child cannot detect the smallest filament after two attempts, the next-largest filament is used.	Objective measure that can evaluate large nerve fiber function.	The test is time-consuming, difficult to conduct in very young children, and requires specialized equipment (monofilaments) and clinician training.
Touch	Large	With the child's eyes closed, brush a cotton ball across the skin in different areas on all extremities. Ask the child to state whether they can feel the cotton ball and where it is being applied. Perform this test bilaterally and move from distal to proximal areas if sensation is reduced.	A non-painful measure of large nerve fiber function. Children enjoy the testing.	The test is time-consuming.
Proprioception	Large	These tests evaluate balance and coordination. Tests that can be used include the finger-to-nose test, thumb-to-finger test, up/down test, and the Romberg test.	A non-painful measure that can evaluate large nerve fiber function. Children enjoy the testing.	It may be difficult to explain the procedure to a child.
Nerve Conduction Studies	Large	Evaluates nerve impulse transmission following electrical stimuli.	Can provide objective information about nerve conduction amplitude and velocity.	The tests are expensive, inconvenient (requires a neurologist referral), and uncomfortable for the child.
Pin-prick Sensation	Small	Ask the child to describe what if feels like when a sharp object (e.g. pin, neuro-tip) is placed on their skin. Perform this test on all extremities. The sensation should be one of pain rather than pressure. Perform this test bilaterally and move from distal to proximal areas if sensation is reduced.	An objective measure that can evaluate small fiber function.	The test is time-consuming and uncomfortable for the child.
Temperature sensation	Small	Use a cool object, such as a metal tuning fork, and place on the child's skin, ask if they feel it as "cold". Perform this test bilaterally and move from distal to proximal areas if sensation is reduced.	The test is quick and easy to conduct and not painful for the child.	It may be difficult for young children to differentiate variations in temperature sensation.

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Am J Cancer Res 2016;6(11):2416-2430

Peripheral Neuropathy

Hyporeflexia

Sensory

Distal to proximal

- Loss proprioceptive and vibration
- Decrease light touch, pinprick, and temperature sensations
- Numbness, tingling, neuropathic pain
- Cranial nerves : hoarseness, jaw pain

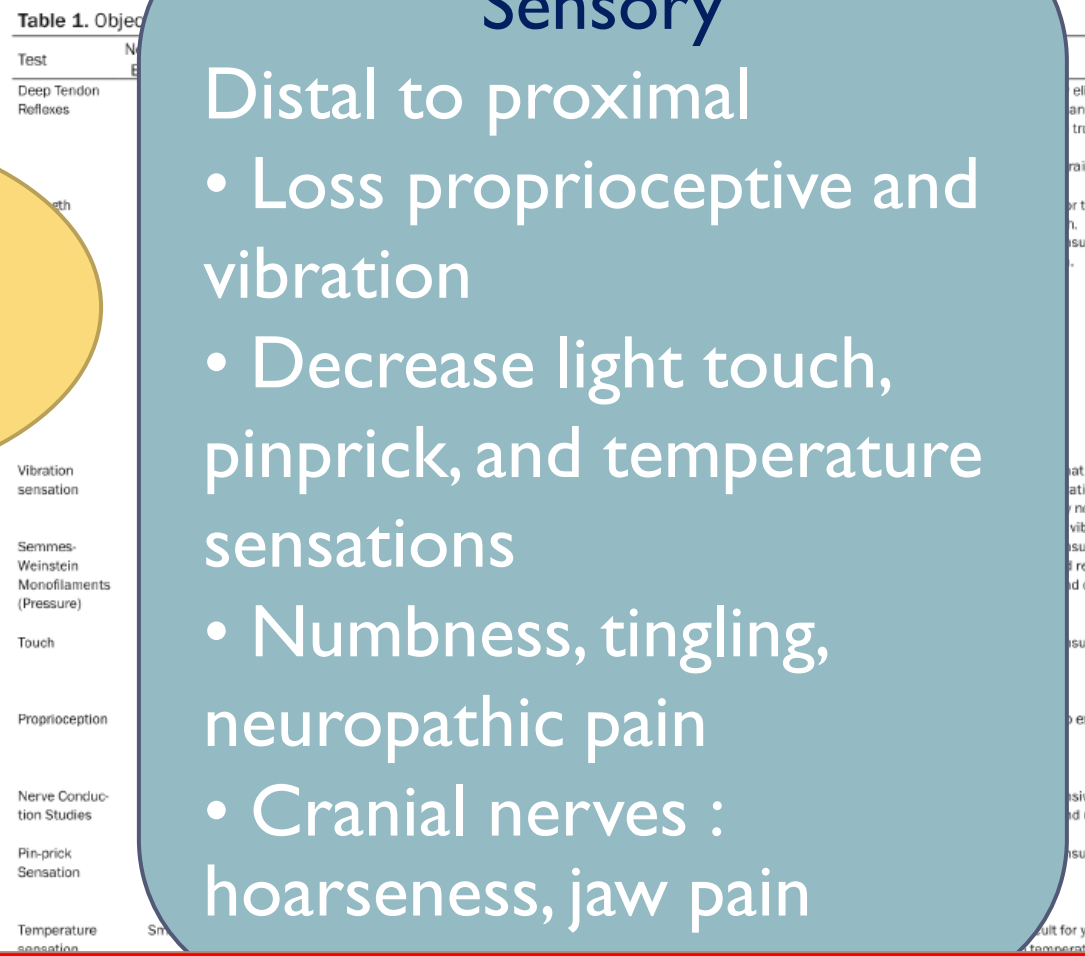


Table 1. Objec

Test	N… B…
Deep Tendon Reflexes	
Vibration sensation	
Semmes-Weinstein Monofilaments (Pressure)	
Touch	
Proprioception	
Nerve Conduction Studies	
Pin-prick Sensation	
Temperature sensation	

Motor

- Foot-drop
- Upper and lower Extremity weakness

Autonomic

- Constipation
- Urinary retention
- Orthostatic hypotension

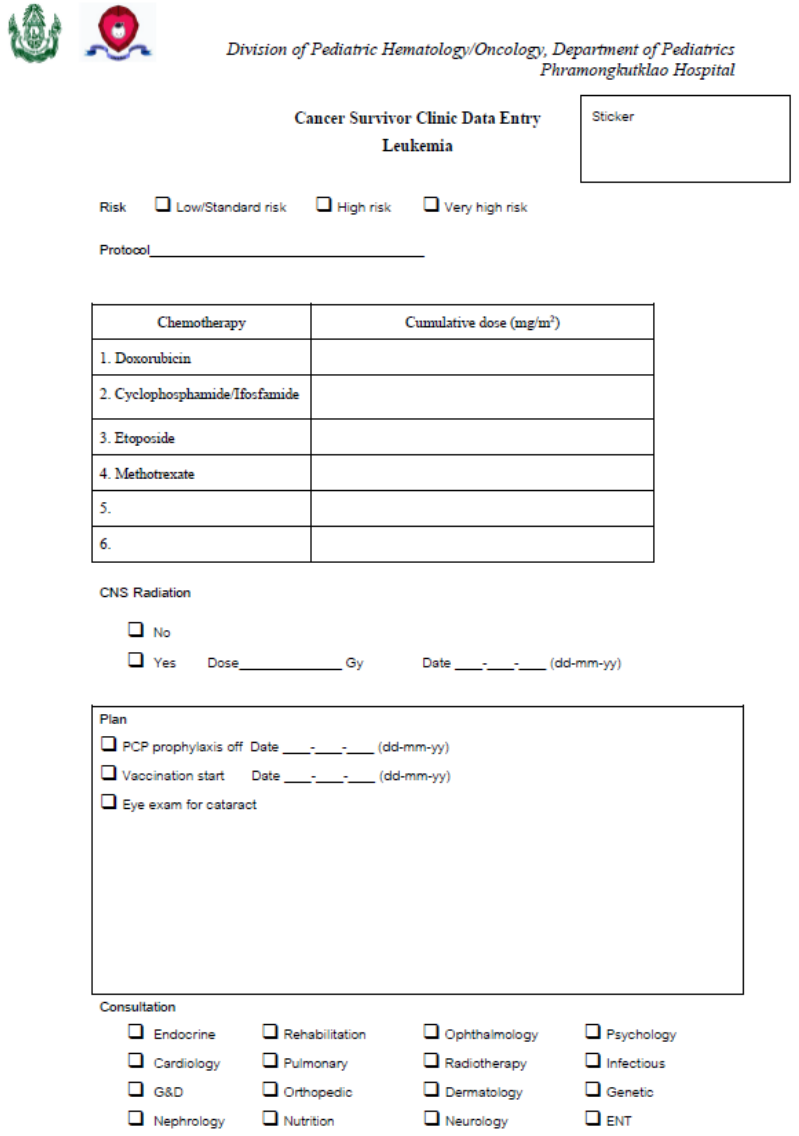
PedHemOnc-PMR

Am J Cancer Res 2016;6(11):2416-2430

Transition to Survival Care

Summary cancer treatment

- Demographic data
- Cancer diagnosis
- Treatment
  - Chemotherapy
  - Radiation
  - HSCT
  - Surgery



Division of Pediatric Hematology/Oncology, Department of Pediatrics
Phramongkutklao Hospital

Cancer Survivor Clinic Data Entry
Leukemia

Sticker

Risk ☐ Low/Standard risk ☐ High risk ☐ Very high risk

Protocol_____

Chemotherapy	Cumulative dose (mg/m²)
1. Doxorubicin	
2. Cyclophosphamide/Ifosfamide	
3. Etoposide	
4. Methotrexate	
5.	
6.	

CNS Radiation

☐ No
☐ Yes Dose_____ Gy Date ___-___-___ (dd-mm-yy)

Plan

☐ PCP prophylaxis off Date ___-___-___ (dd-mm-yy)
☐ Vaccination start Date ___-___-___ (dd-mm-yy)
☐ Eye exam for cataract

Consultation

☐ Endocrine	☐ Rehabilitation	☐ Ophthalmology	☐ Psychology
☐ Cardiology	☐ Pulmonary	☐ Radiotherapy	☐ Infectious
☐ G&D	☐ Orthopedic	☐ Dermatology	☐ Genetic
☐ Nephrology	☐ Nutrition	☐ Neurology	☐ ENT

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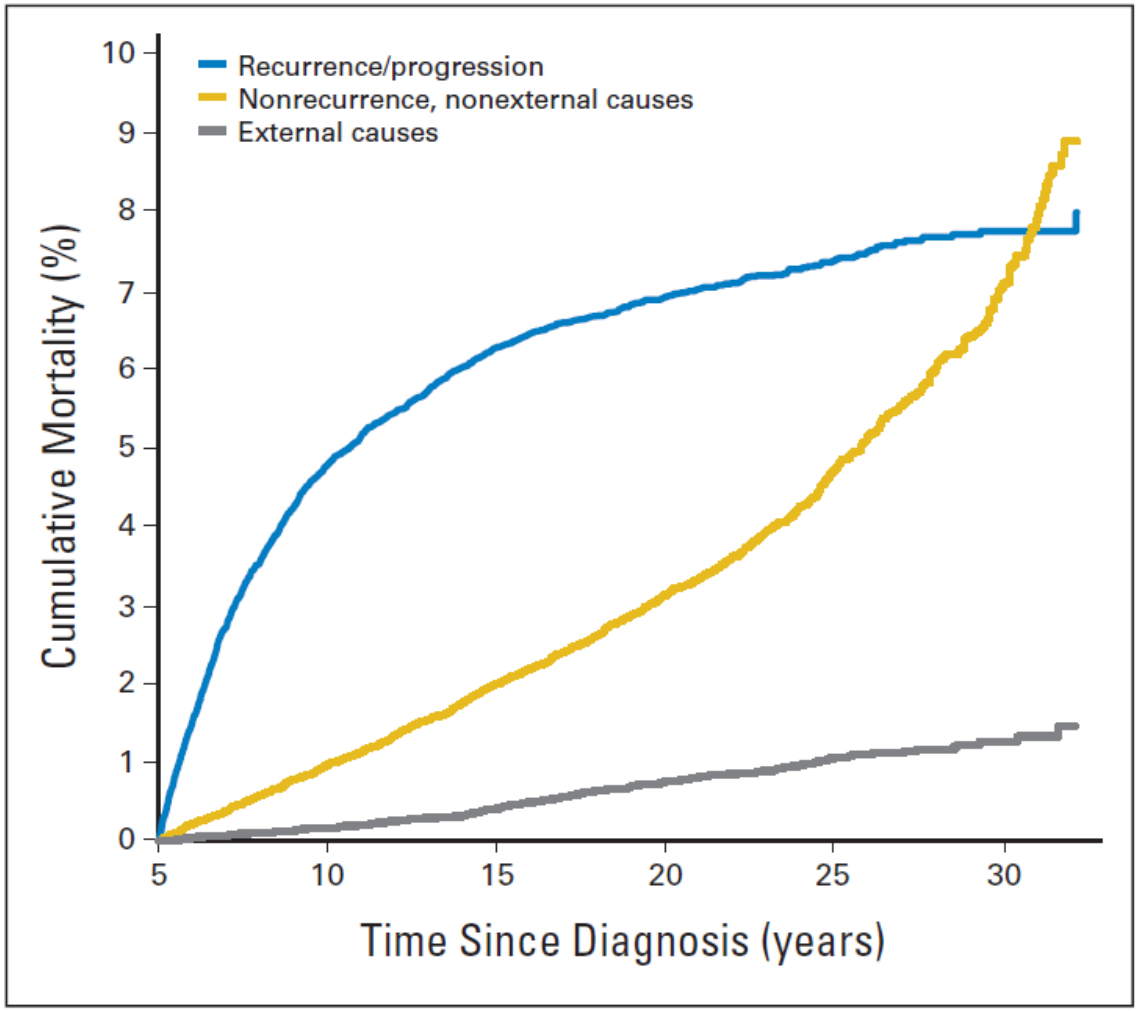
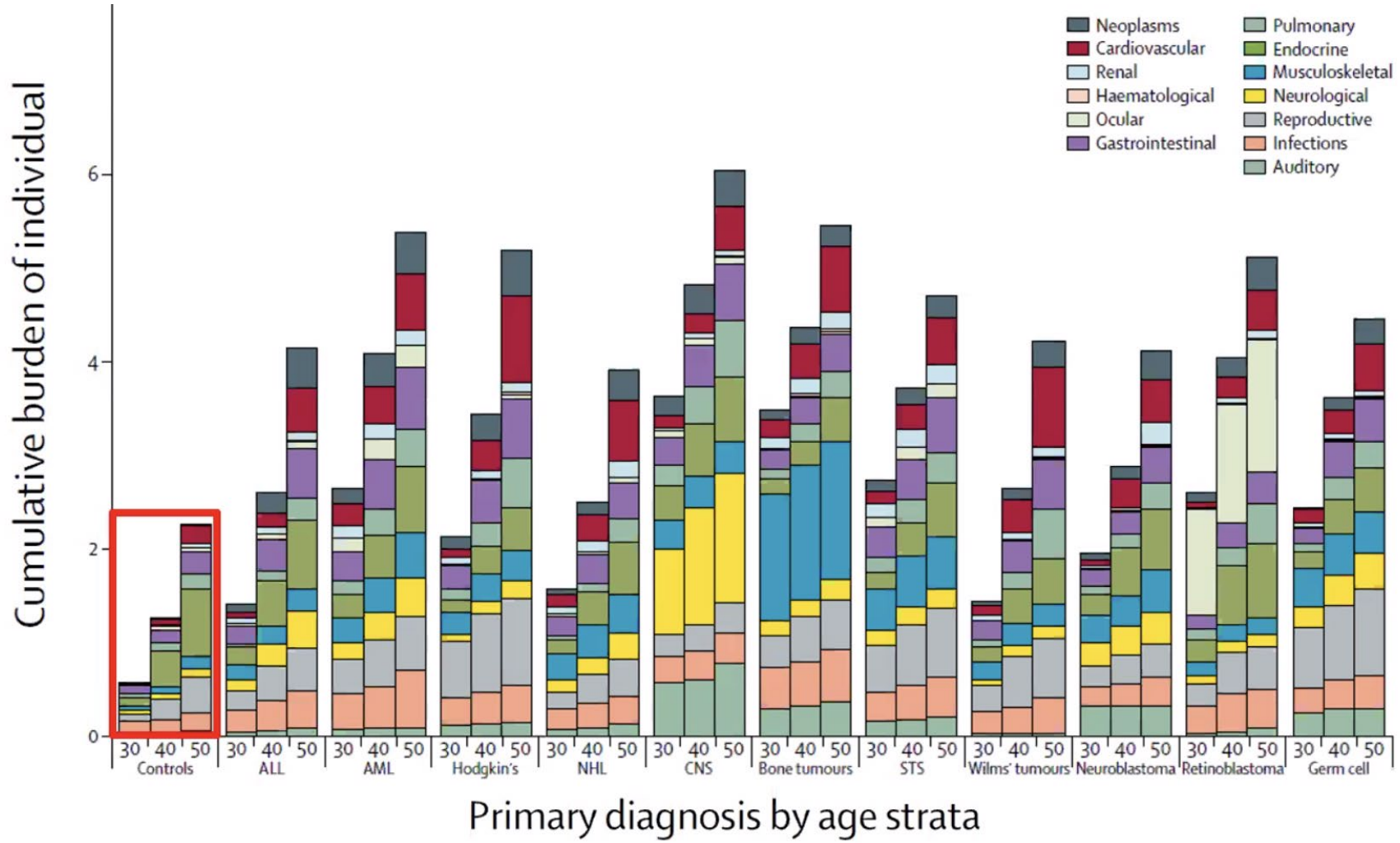
CANCER SURVIVOR CLINIC

Cumulative Cause-Specific Mortality



Armstrong GT, et al. Journal of Clinical Oncology. 2009 May 10;27(14):2328.

Grades 3-5 Chronic Health Conditions



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Bhakta N, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). Lancet. 2017 Dec 9;390(10112):2569-2582.

Top 5 Ranks of Late Effects from Chinese Children's Cancer Group (CCCG)

- Osteonecrosis and osteoporosis
- Left ventricular dysfunction
- CNS SMN and secondary AML
- Gonadal dysfunction and GH deficiency
- Neurocognitive deficits

Cheung YT, et al. Identifying Priorities for Harmonizing Guidelines for the Long-Term Surveillance of Childhood Cancer Survivors in the Chinese Children Cancer Group (CCCG). JCO Glob Oncol. 2021

Int J Hematol (2010) 91:850–854
DOI 10.1007/s12185-010-0594-9

ORIGINAL ARTICLE

Late effects in survivors of childhood acute lymphoblastic leukemia: a study from Thai Pediatric Oncology Group

Samart Pakakasama · Gavivann Veerakul · Darin Sosothikul · Su-on Chainansamit · Vichai Laosombat · Pattra Thanarattanakorn · Rachata Lumkul · Surapon Wiangnon · Somporn Wangruangsathit · Nattee Narkbunnam · Somjai Kanjanapongkul

Late effects	Number (%) ($n = 258$)
Endocrine/metabolic	64 (24.8)
Psychosocial	28 (10.9)
Cardiovascular	9 (3.5)
Dental	5 (1.9)
Nervous system	4 (1.5)
Dermatologic	2 (0.8)
Immune	2 (0.8)
Pain	2 (0.8)
Auditory	2 (0.8)
Gastrointestinal/hepatic	1 (0.4)
Ocular	1 (0.4)
Musculoskeletal	1 (0.4)
Pulmonary	0
Urinary	0

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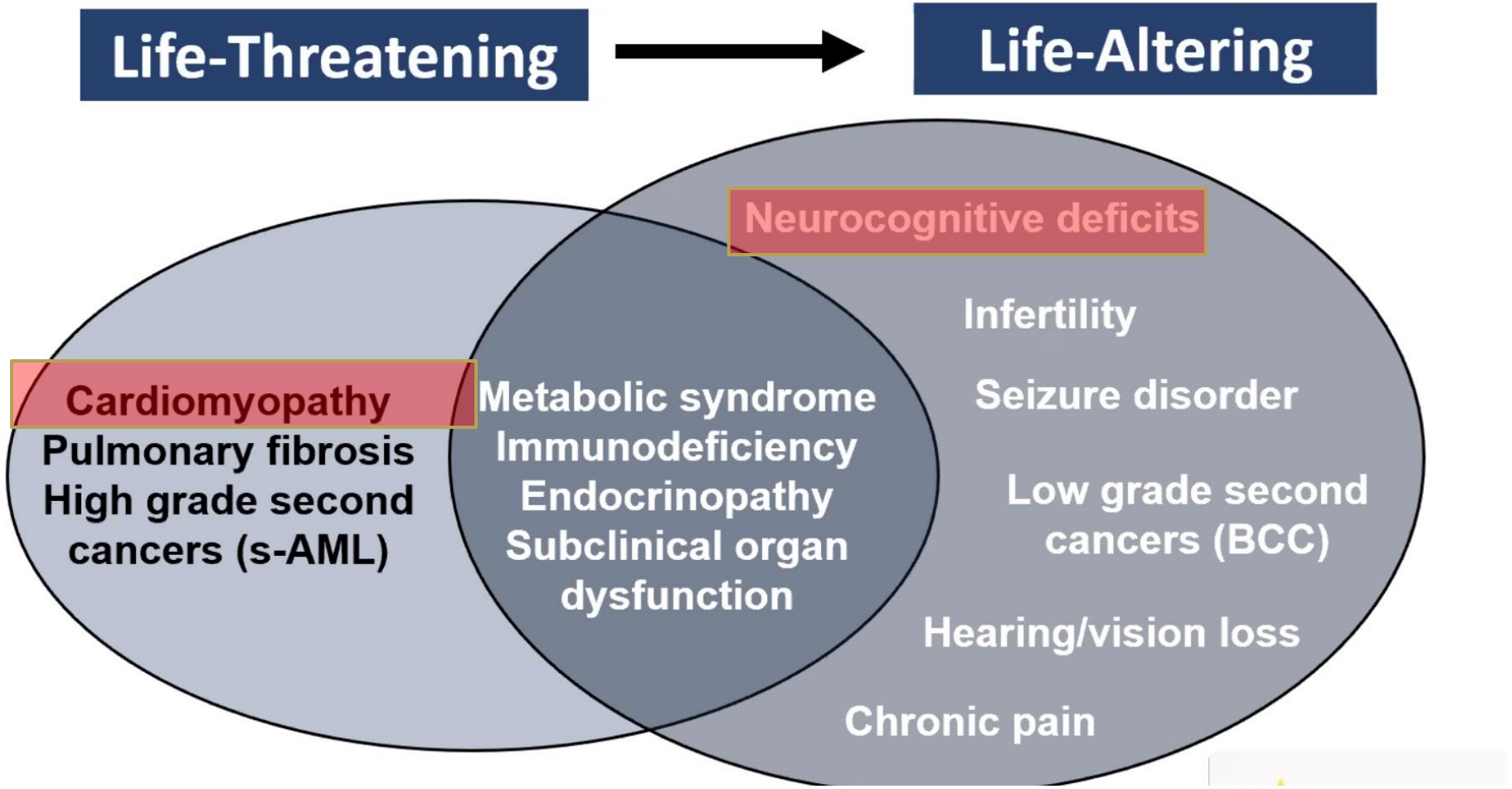
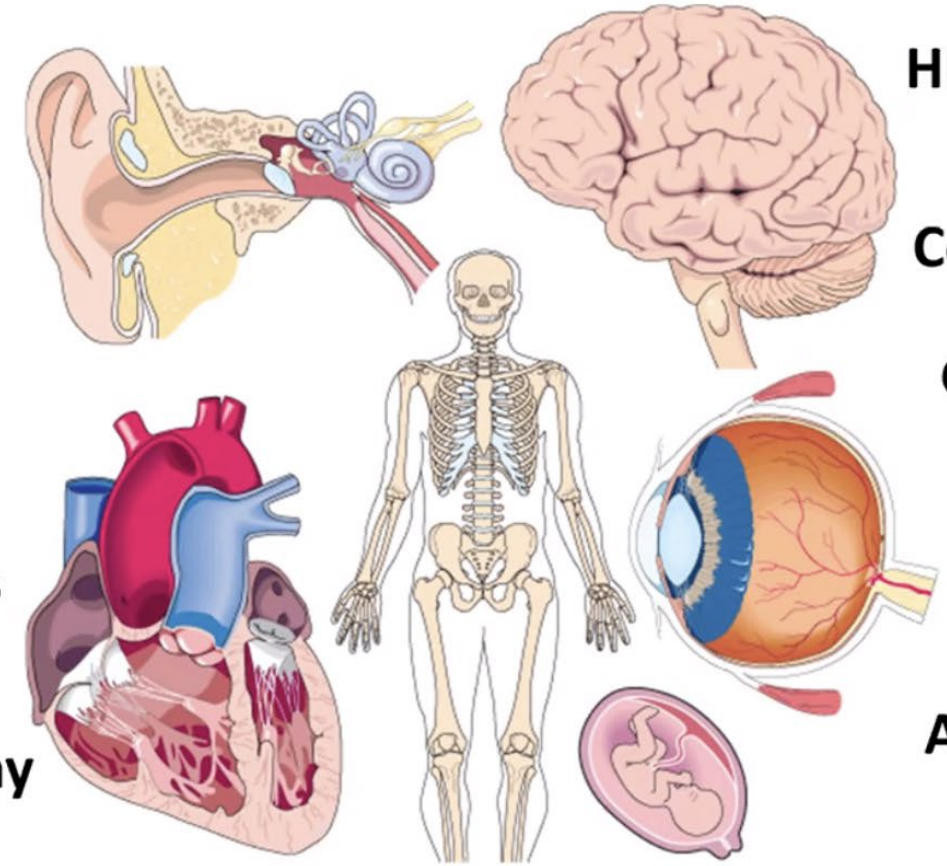
Evolving Spectrum of Late Effects



Chemotherapies VS. Toxicities



Cisplatin → Hearing loss

HD Methotrexate → Cognitive decline

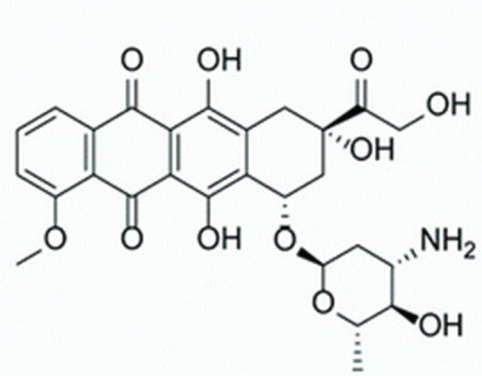
Anthracyclines → Cardiomyopathy

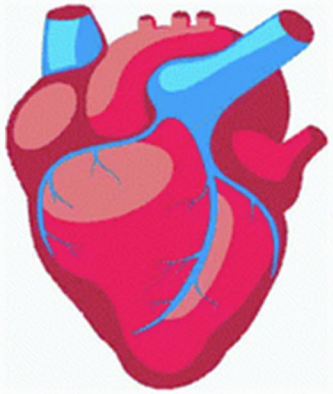
Glucocorticoids, Busulfan → Cataracts

Alkylating agents → Infertility

Glucocorticoids → Osteoporosis, Osteonecrosis

Doxorubicin Induced Cardiotoxicities

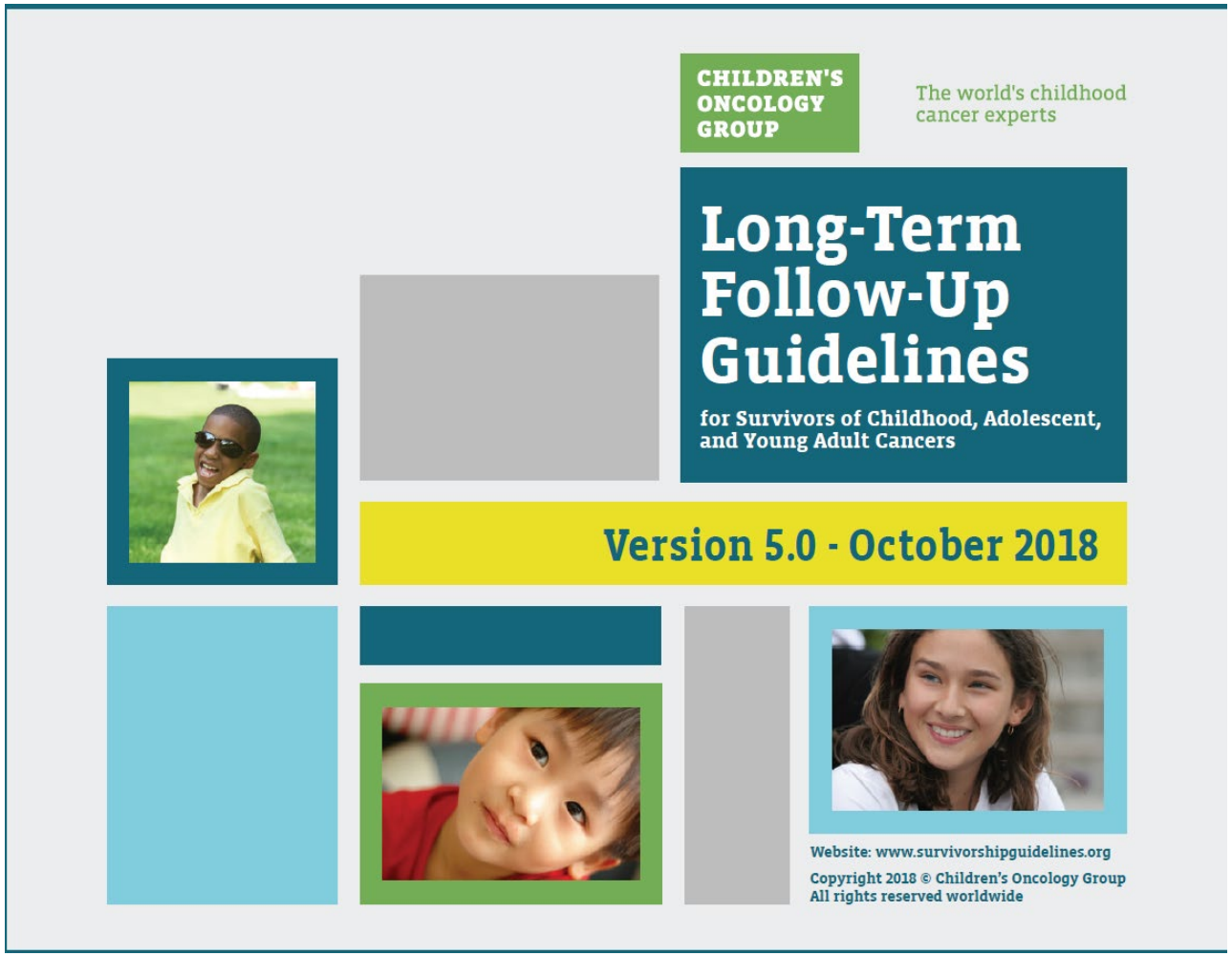




Acute Cardiotoxcicity → Early Stage Chronic Cardiotoxcicity → Late Stage Chronic Cardiotoxcicity

High **Cardiotoxicity Reversibility** Low

Qin Y, Guo T, Wang Z, Zhao Y. Journal of Materials Chemistry B. 2021.



Recommended Frequency of Echocardiogram		
Anthracycline Dose*	**Radiation Dose****	**Recommended Frequency**
None	< 15 Gy or none	No screening
	≥ 15 - < 35 Gy	Every 5 years
	≥ 35 Gy	Every 2 years
< 250 mg/m²	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m²	Any or none	Every 2 years

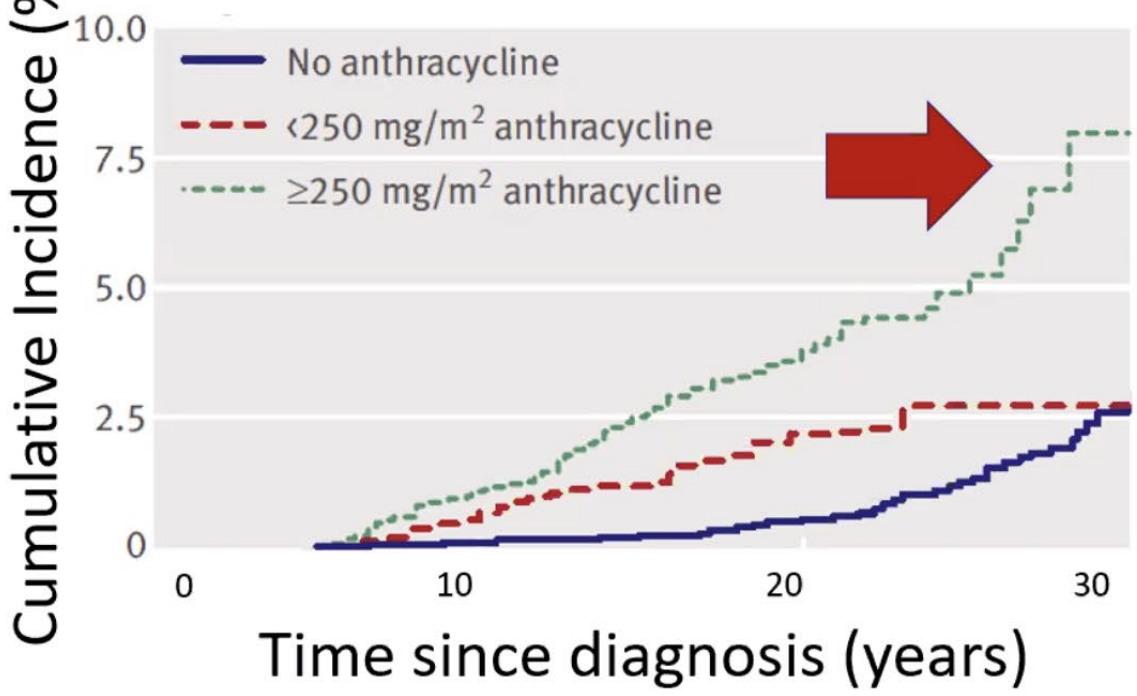
*Based on doxorubicin isotoxic equivalent dose. See dose conversion instructions in section 33.
**Based on radiation dose with potential impact to heart (radiation to chest, abdomen, spine [thoracic, whole], TBI). See section 76.

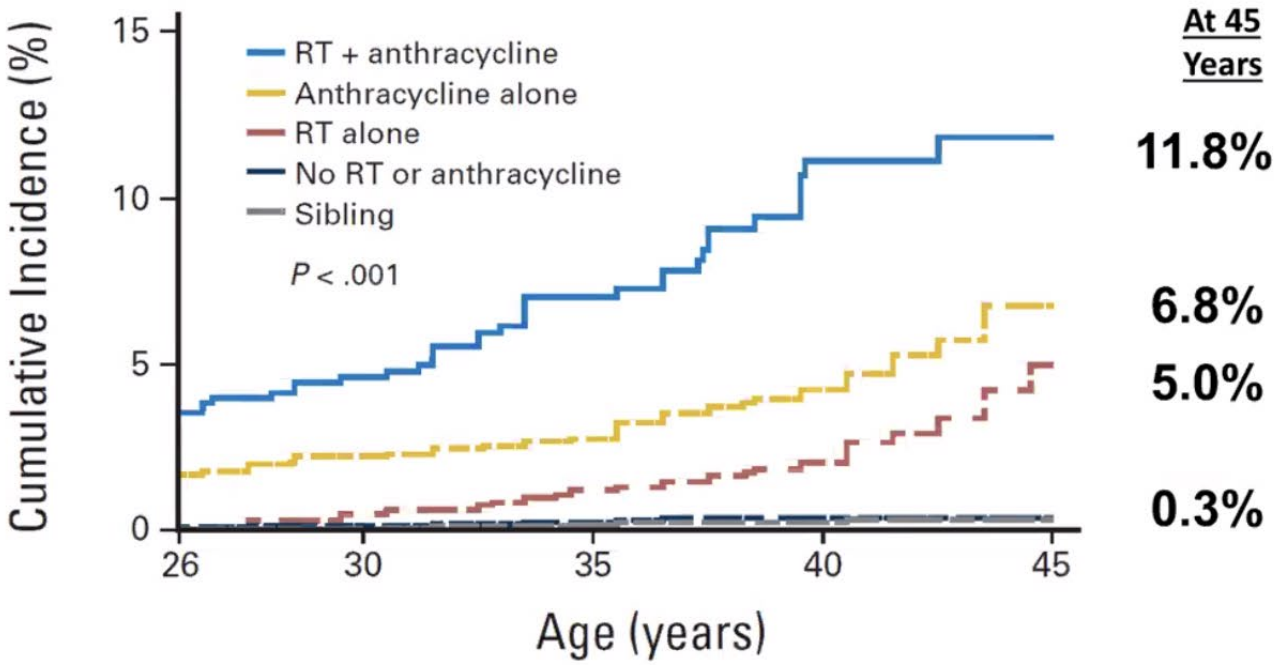
Anthracyclins	Formula
Doxorubicin	x 1
Mitoxantrone	x 4
Idurubicin	x 5
Daunorubicin	x 0.833

Dose and Therapy Combinations after Risk of Late Effects

Dose response relationship in heart failure

- 2.4-fold after < 250 mg/m^2
- 5.2-fold after >= 250 mg/m^2



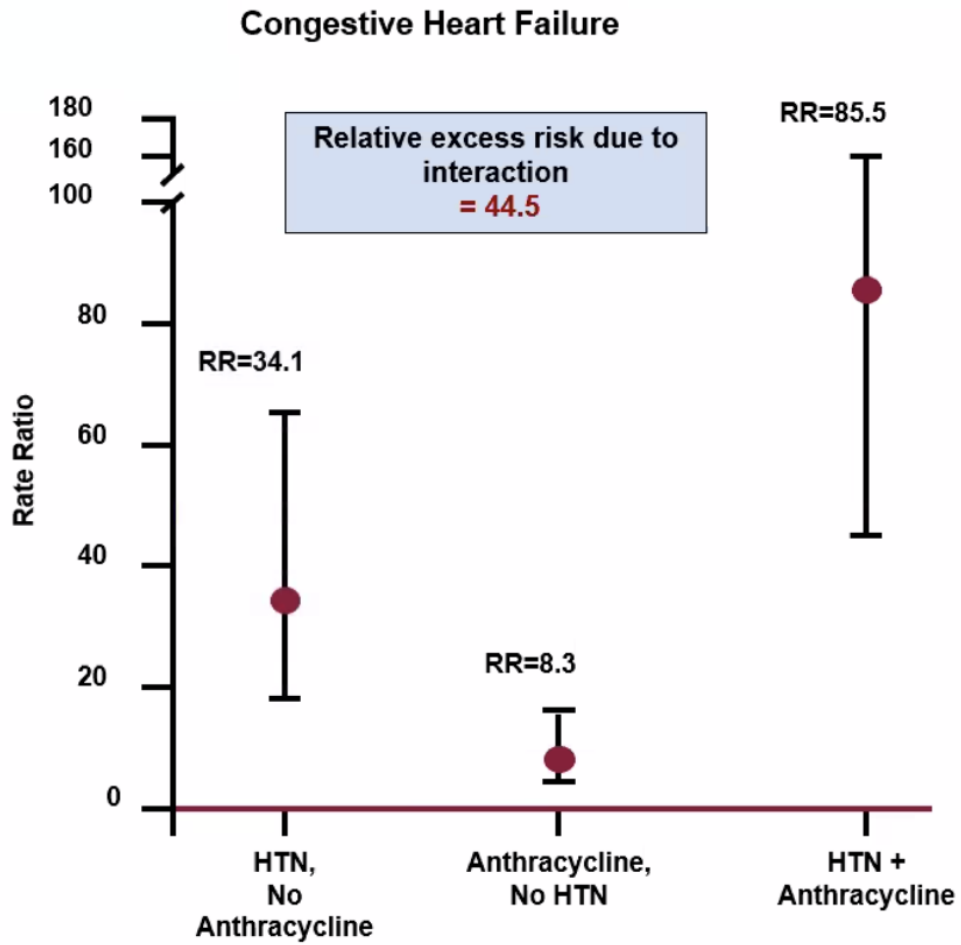


Risk of heart failure and other major cardiac events was associated with exposure to anthracycline chemotherapy and chest-directed radiation in a dose-dependent manner.

Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the CCSS cohort. *BMJ.* 2009;339:b4606

Armstrong GT, Oeffinger KC, Chen Y, et al. Modifiable risk factors and cardiac events among adult survivors of childhood cancer. *J Clin Oncol.* 2013;31(29):3673-3680

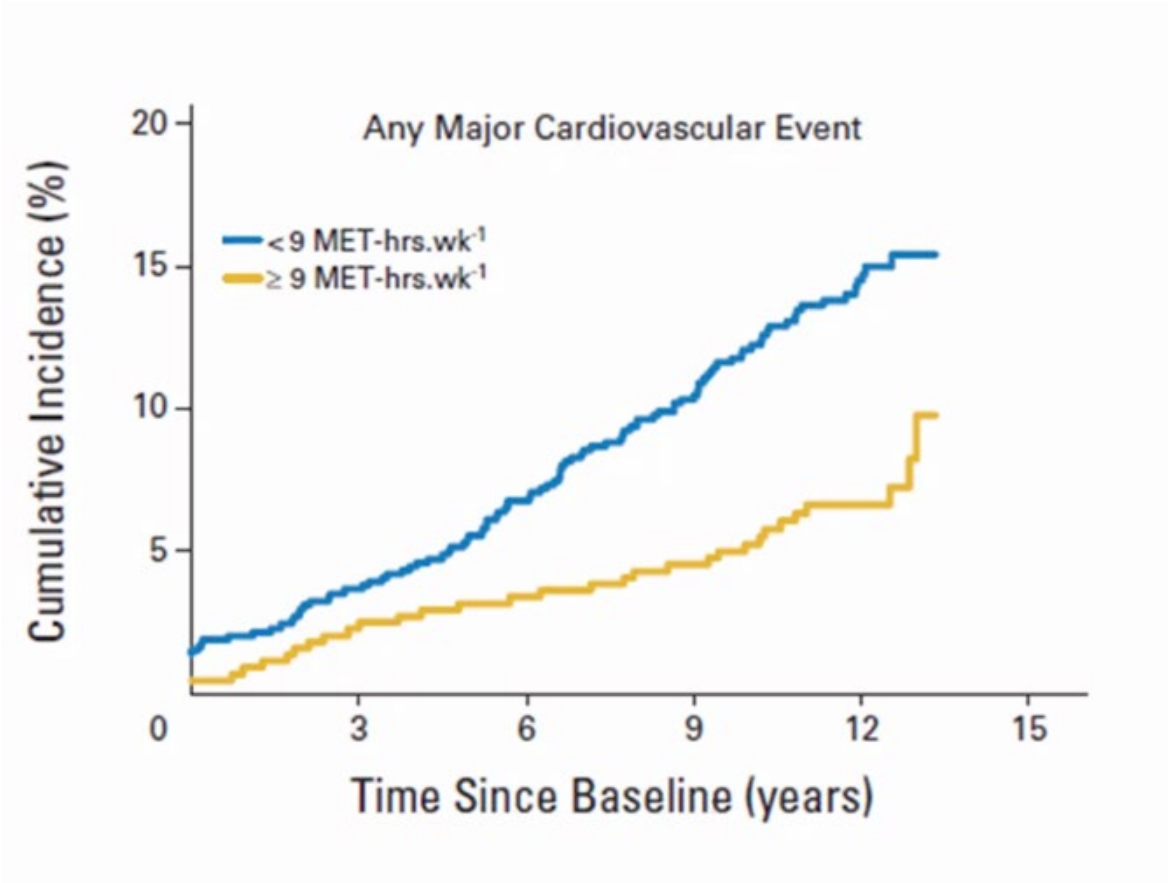
Comorbidities and CHF Late Effects



- Hypertension potentiates anthracycline-associated risk of CHF in childhood cancer survivors.
- CVD risk factors increase risk of CHF.
- Prevention of hypertension should be focus during survivorship care.

Armstrong GT, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol. 2013 Oct 10;31(29):3673-80.

Health Habits Associated Late Effects



- Vigorous exercise was associated with dose-dependent lower risk of CVE
- Risk was independent of CV risk profile among childhood HL

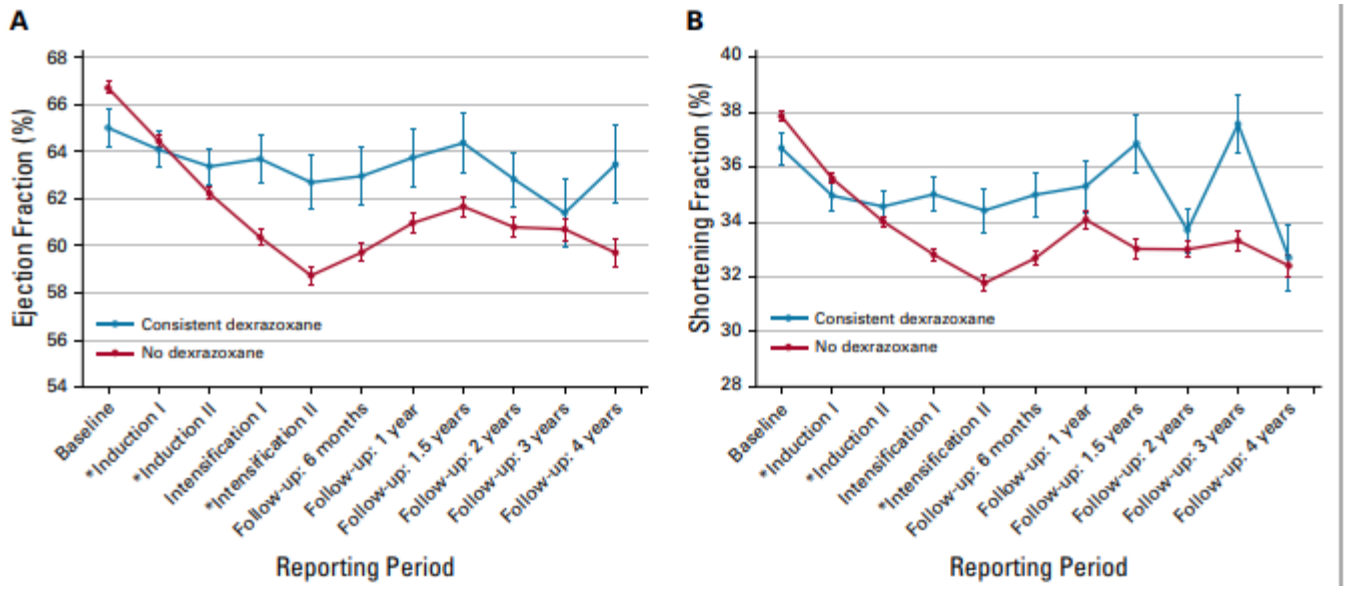
Jones LW, et al. Exercise and risk of major cardiovascular events in adult survivors of childhood hodgkin lymphoma: a report from the childhood cancer survivor study. J Clin Oncol. 2014 Nov 10;32(32):3643-50.

Check for updates

original reports

Effect of Dexrazoxane on Left Ventricular Systolic Function and Treatment Outcomes in Patients With Acute Myeloid Leukemia: A Report From the Children's Oncology Group

Kelly D. Getz, PhD, MPH[1,2]; Lillian Sung, MD, PhD[3]; Todd A. Alonzo, PhD[4]; Kasey J. Leger, MD, MS[5]; Robert B. Gerbing, BS, MA[6]; Jessica A. Pollard, MD[7]; Todd Cooper, DO[5]; E. Anders Kolb, MD[8]; Alan S. Gamis, MD, MPH[9]; Bonnie Ky, MD, MSCE[2]; and Richard Aplenc, MD, MSCE[1,2]



Pediatric Cancer & Hematologic Disorder
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J Clin Oncol 38:2398-2406

Original Article

Late Health Outcomes After Dexrazoxane Treatment: A Report From the Children's Oncology Group

Eric J. Chow, MD, MPH [1]; Richard Aplenc, MD, PhD[2]; Lynda M. Vrooman, MD[3]; David R. Doody, MS[1]; Yuan-Shung V. Huang, MS[2]; Sanjeev Aggarwal, MD[4]; Saro H. Armenian, DO, MPH [5]; K. Scott Baker, MD, MS[1]; Smita Bhatia, MD, MPH [6]; Louis S. Constine, MD[7]; David R. Freyer, DO, MS[8]; Lisa M. Kopp, DO, MPH[9]; Wendy M. Leisenring, ScD [1]; Barbara L. Asselin, MD[7]; Cindy L. Schwartz, MD, MPH [10]; and Steven E. Lipshultz, MD[11]

- N=1308; ALL, HD, osteosarcoma
- ALL-Accumulate doxorubicin100-360 mg/m^2:Dexrazoxane was not associated with relapse, second cancers, all-cause mortality, or cardiovascular mortality.
- ALL: cardiovascular outcomes (cardiomyopathy, ischemic heart disease, and stroke) occurred less commonly with dexrazoxane (5.6%) than without it (17.6%; *P* = .02), although cardiomyopathy rates alone did not differ (4.4% vs 8.1%; *P* = .35)
- Among OS patients exposed to dexrazoxane; cumulative doxorubicin, 450-600 mg/m^2 ; median F/U, 16.6-18.4 years, no cardiovascular deaths or heart transplantation occurred.

Chow EJ, et al. Cancer. 2021 Oct 13. doi: 10.1002/cncr.33974. Epub ahead of print.

Reduced Cardiotoxicity of Doxorubicin by a 6-Hour Infusion Regimen

A Prospective Randomized Evaluation

J. SHAPIRA, MD, M. GOTFRIED, MD, M. LISHNER, MD, AND M. RAVID, MD

In order to evaluate the possible cardiosparing effect of a prolonged infusion of doxorubicin as compared with the standard mode of administration 62 consecutive patients with metastatic carcinoma of the breast or carcinoma of the ovary Stage III or IV were prospectively randomized to receive doxorubicin either as a rapid infusion over 15 to 20 minutes at 8 AM or as a continuous infusion over 6 hours, 8 AM to 2 PM. The remaining protocol was identical for the two groups. The cardiotoxic effect of doxorubicin was evaluated by history and physical examination and by the decline in resting ventricular ejection fraction (LVEF) as determined by gated pool radionuclide angiography with technetium 99m (^{99m}Tc) and by the decline in the height of the QRS complexes in the standard leads of the echocardiogram (ECG). Initially there were 31 patients in each group. The cumulative dose of doxorubicin, was 410 mg/m^2 ± 42 SD in the standard infusion group and 428 mg/m^2 ± 48 SD in the 6-hour infusion group. The mean decline in LVEF after a cumulative doxorubicin dose of 300 mg/m^2 was 17% in the first group and only 4.1% in the second. After 400 mg/m^2 the mean fall in LVEF was 21% in the first group and 6% in the second. The mean decline in QRS voltage after 300 mg/m^2 was 29% and 1.5%, respectively. Four patients, all in the standard infusion group, developed congestive heart failure. These data suggest that slow infusion of doxorubicin is associated with reduced cardiotoxicity.

Cancer 65:870–873, 1990.

Pediatric Cancer & Hematologic Disorder
PedHemOnc-PMK

Current Oncology Reports (2020) 22: 72
https://doi.org/10.1007/s11912-020-00923-w

CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Check for updates

Cardioprotective Strategies to Prevent Cancer Treatment-Related Cardiovascular Toxicity: a Review

Jenica N. Upshaw[1]

Published online: 20 June 2020
© Springer Science+Business Media, LLC, part of Springer Nature 2020

Table 1 Cardiovascular effects of cancer therapy and cardioprotective strategies

Cancer therapy	Cardiovascular (CV) risk	Cardioprotective agents
Anthracycline	Heart failure, CV death, arrhythmias	RCTs (clinical endpoints): dexrazoxane, continuous infusion, liposomal formulations RCTs (surrogate endpoints): neurohormonal antagonist therapy (LVEF), exercise (VO2 max) Ongoing studies: statins

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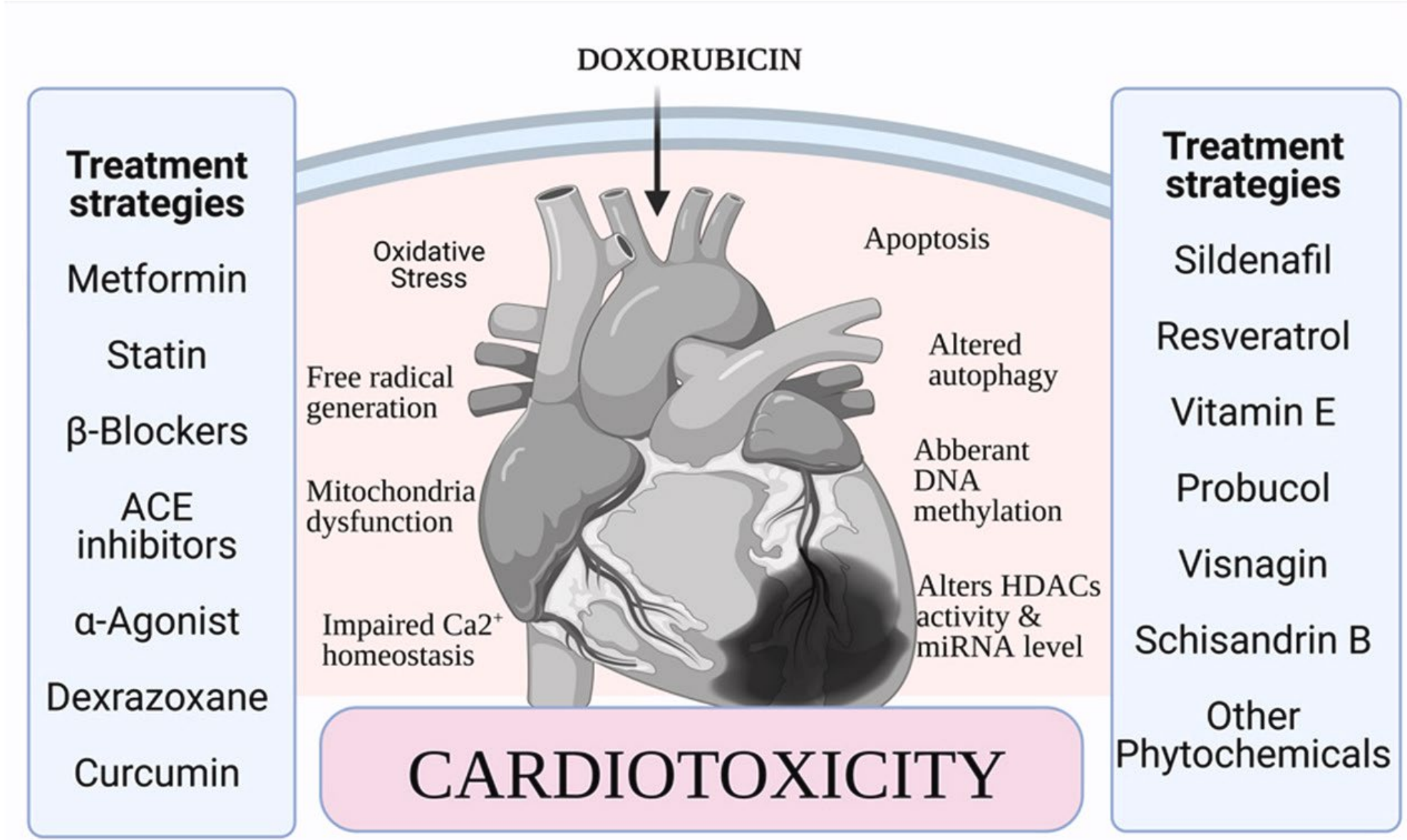

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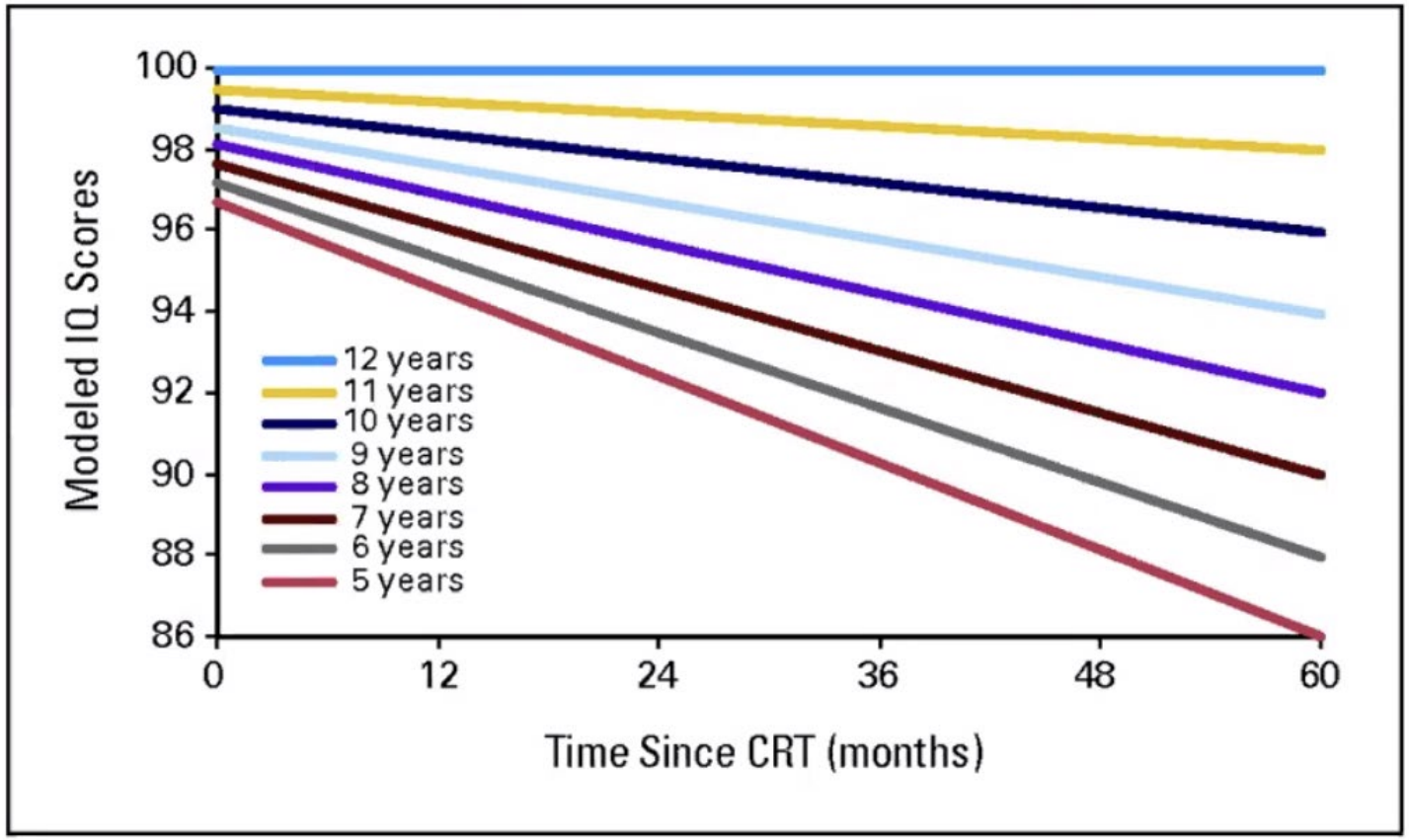
Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U. Biomedicine & Pharmacotherapy. 2021 Jul 1;139:111708.

Age at Diagnosis Influences Vulnerability



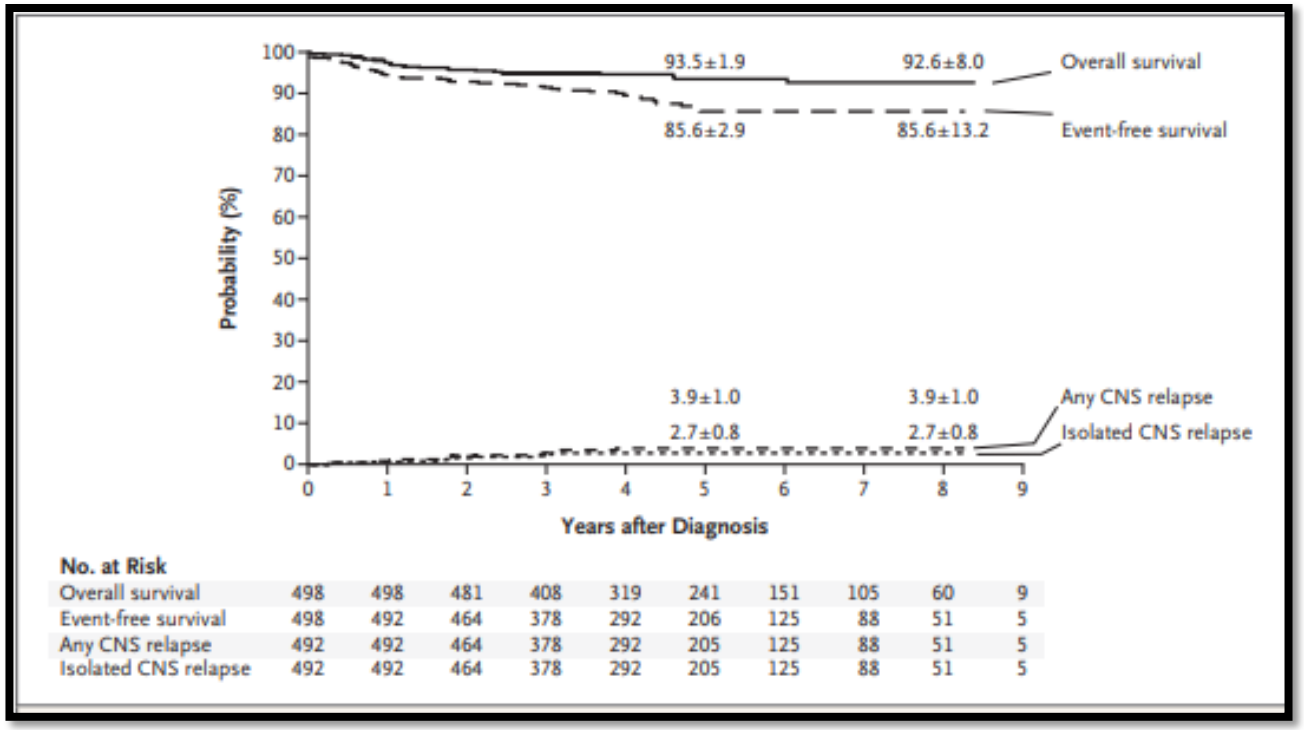
Merchant TE, et al. Late effects of conformal radiation therapy for pediatric patients with low-grade glioma: prospective evaluation of cognitive, endocrine, and hearing deficits. J Clin Oncol. 2009 Aug 1;27(22):3691-7.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treating Childhood Acute Lymphoblastic Leukemia without Cranial Irradiation

Ching-Hon Pui, M.D., Dario Campana, M.D., Ph.D., Deqing Pei, M.S., W. Paul Bowman, M.D., John T. Sandlund, M.D., Sue C. Kaste, D.O., Raul C. Ribeiro, M.D., Jeffrey E. Rubnitz, M.D., Ph.D., Susana C. Raimondi, Ph.D., Mihaela Onciu, M.D., Elaine Coustan-Smith, M.S., Larry E. Kun, M.D., Sima Jeha, M.D., Cheng Cheng, Ph.D., Scott C. Howard, M.D., Vickey Simmons, R.N., Amy Bayles, C.P.N.P., Monika L. Metzger, M.D., James M. Boyett, Ph.D., Wing Leung, M.D., Ph.D., Rupert Handgretinger, M.D., James R. Downing, M.D., William E. Evans, Pharm.D., and Mary V. Relling, Pharm.D.



No. at Risk

Overall survival	498	498	481	408	319	241	151	105	60	9
Event-free survival	498	492	464	378	292	206	125	88	51	5
Any CNS relapse	492	492	464	378	292	205	125	88	51	5
Isolated CNS relapse	492	492	464	378	292	205	125	88	51	5

Pediatric Cancer & Hematologic Disorder
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Pui CH, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med. 2009 Jun 25;360(26):2730-41

VOLUME 24 · NUMBER 24 · AUGUST 20 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Comparison of Long-Term Neurocognitive Outcomes in Young Children With Acute Lymphoblastic Leukemia Treated With Cranial Radiation or High-Dose or Very High-Dose Intravenous Methotrexate

Brenda J. Spiegler, Kimberly Kennedy, Ronnen Maze, Mark L. Greenberg, Sheila Weitzman, Johann K. Hitzler, and Paul C. Nathan

Table 5. Neurocognitive Outcomes After CRT Versus Chemotherapy Alone

	Population Norm		Chemotherapy* (n = 54)		CRT (n = 25)		
	Mean	SD	Mean	SD	Mean	SD	*P*†
Intelligence							
Verbal comprehension	100	15	99.5	10.27	89.8	10.4	.0003
Perceptual organization	100	15	102.9	14.4	88.7	14.5	.0002
Freedom from distractibility	100	15	98.4	13.0	88.2	10.6	.0011
Processing speed	100	15	104.9	14.1	90.8	14.8	.0001
Attention							
Delay	0.0	1.0	−.74	1.4	−.60	1.2	.73
Vigilance	0.0	1.0	−.31	1.4	−.41	1.3	.78
Distractibility	0.0	1.0	−.17	1.6	−.18	1.1	.98
Memory							
Visual immediate	100	15	100.7	13.1	93.3	10.8	.03
Visual delay	100	15	103.0	10.5	90.4	12.4	.0001
Verbal immediate	100	15	100.0	14.4	91.2	10.1	.017
Verbal delay	100	15	101.1	14.7	94.4	9.0	.065
Attention/concentration	100	15	101.6	13.3	90.2	14.2	.0026
General memory index	100	15	102.8	15.1	88.2	12.3	.0011
Academics							
Single-word reading	100	15	102.9	9.7	95.3	14.8	.009
Reading decoding	100	15	102.2	8.0	95.6	13.0	.009
Reading comprehension	100	15	101.3	9.9	89.2	11.8	< .0001
Spelling	100	15	101.9	12.5	94.3	13.2	.0172
Arithmetic	100	15	96.4	14.5	89.5	11.9	.047

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Intraocular Heterotropic Ossification

- Eyeball structures ossification is a rare type of metaplasia
- Ectopic bone formation can be found in any soft, highly vascularized tissue
- The study examined 2,486 enucleated eyes, intraocular ossification was found in only 119 cases (4.8%) 67% were from men, 32% were from women

Pediatric Cancer & Hematologic Disorder
PedHemOncPMK

Am J Ophthalmol 1969; 68: 683-90
Rom J Ophthalmol. 2017 Jan-Mar; 61(1): 65–68

Intraocular Heterotropic Ossification

- A 70-year-old Caucasian man, asymptomatic lymphoplasmacytic lymphoma, presented with a blind painful right eye to evaluate enucleation bulbi.
- Histopathologic examination revealed ossification with intertrabecular infiltration in the metaplastic bone marrow of non-Hodgkin B lymphoma, with small lymphocytes
- Careful histopathological examination in patients with a history of malignant neoplastic pathology is necessary to confirm the diagnosis and exclude occult malignancies

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J Med Case Rep. 2020; 14: 92.

Lesson Learn!

- Role of regular eye examinations in leukemic patients especially in
  - Hyperleukocytosis
  - CNS involvement
  - Multiple episodes of neutropenia
- Eye examination could be performed at the date at diagnosis for baseline and at the end of treatment.
- Regular eye examination may be a crucial role to diagnostic and prevention among those patients.

Summary

- Increased survival, increased late effect, need closely monitor
- Minimized cardiologic toxicities
  - Monitor BP
  - Health behaviors
  - Rationale use of anthracyclines
  - Minimized RT
  - Follow-up with echocardiogram

Summary

- Minimized neurologic toxicities
  - Monitor BP: beware PRES
  - Carefully treating patients with HD-MTX, IT CMT
  - Monitor MTX level
  - DTR when treating patients with VCR
  - Omit CNS RT -> HD-MTX
  - Regular eye examination in CNS+, hyperleukocytosis leukemia


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