Life after Cancer:

Surveillance and Management of Chronic Health Conditions after Treatment for Childhood Cancer

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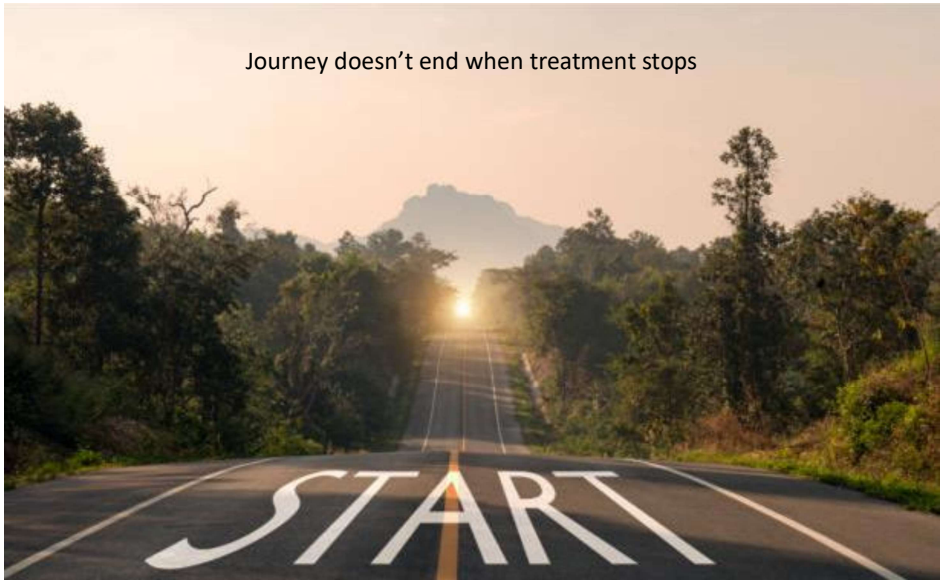
November 2024

Overview

1. Introduce Cancer as a Chronic Condition, and the role of secondary and tertiary surveillance of late effects after childhood cancer
2. Review the risk factors, manifestations, and screening recommendations for the most common late effects
3. Discuss the psychosocial impact of childhood cancer treatment
4. Share resources and tools available to guide care of a pediatric cancer survivor
5. Explore Models of Care for surveillance and management of chronic health conditions

Cancer as a Chronic Disease

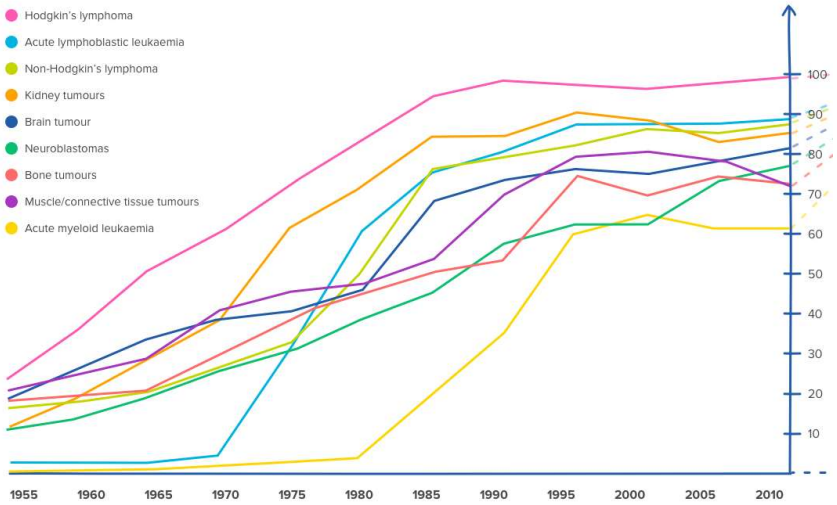


“In the years since I finished my treatment, I have seen many doctors and the biggest thing that all my doctors say is that I am 'all better' but really with such a big thing happening to me even when the thing harming you is gone there is still the damage […] and for most cases it doesn't fully go away, or heal all the way and for most people that can mean some side effects. [...] that it is something that in my opinion i think that it is important to acknowledge when talking to a patient.”

- 9 years since completed treatment for rhabdomyosarcoma

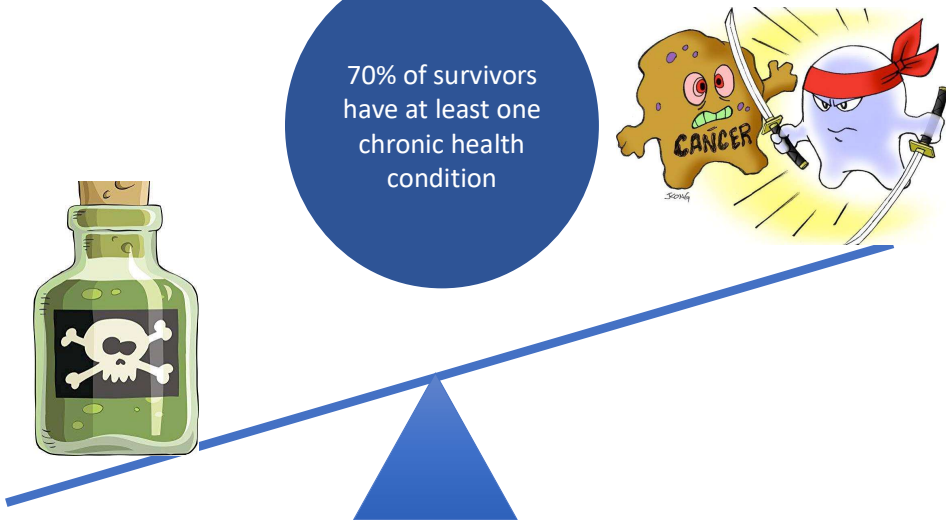
Survival for Childhood Cancer

Average 5-year survival
84%



Cost of Cure

70% of survivors have at least one chronic health condition



Cohort Studies

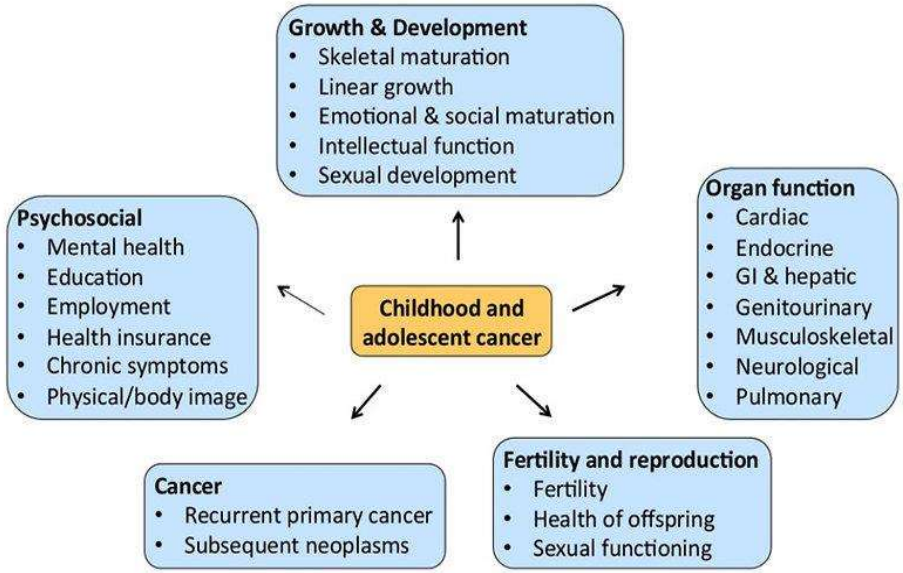
CCSS

Childhood Cancer Survivor Study

St. Jude Children's Research Hospital

St. Jude LIFE Study

Childhood, Adolescent and Young Adult Cancer Survivors Program (CAYACS)



Late Effects of Chemotherapy

Chemotherapy	Special Late Effects
Cyclophosphamide	Cystitis Infertility >7.5 g/m2 Secondary malignancy (bladder, AML)
Ifosfamide	Tubulopathies Infertility >60 g/m2
Etoposide	Secondary AML (Early - < 3 y post)
Cisplatin/Carboplatin	Ototoxicity Nephrotoxicity
Cytarabine (High dose IV)	Neurocog deficits (LD, lower IQ, behaviour) Cerebellar dysfunction
BCNU/CCNU	Pulmonary fibrosis Secondary AML
Bleomycin	Pulmonary fibrosis Risk of ARDS or lung injury with reactive oxygen species
Steroids	Reduced bone density Avascular necrosis of bone Cataracts
Doxorubin/ Daunorubicin	Cardiomyopathy (CHF, dilated CM) Valvular disease Secondary AML
Methothrexate	Cognitive impairment ADHD

17 year old relapsed ALL at age of 2 years, treated with bone marrow transplantation with 400 TBI + testicular RT

- Left ventricular dysfunction
- Chronic kidney disease
- Moderate obstructive lung disease
- Short stature
- Scoliosis
- GH deficiency
- Atypical dental eruptions
- Cataracts
- Testosterone deficiency
- Hypothyroidism
- Thyroid nodules
- Liver nodules
- Low-average IQ
- Learning disability in math and writing
- Poor working memory and attention
- Depression, social anxiety
- Azoospermia & infertility

Journey of Survivor – Early years

CURED!

Fear of relapse

Acute complications of treatment

Rehab

Adjusting to “normal”

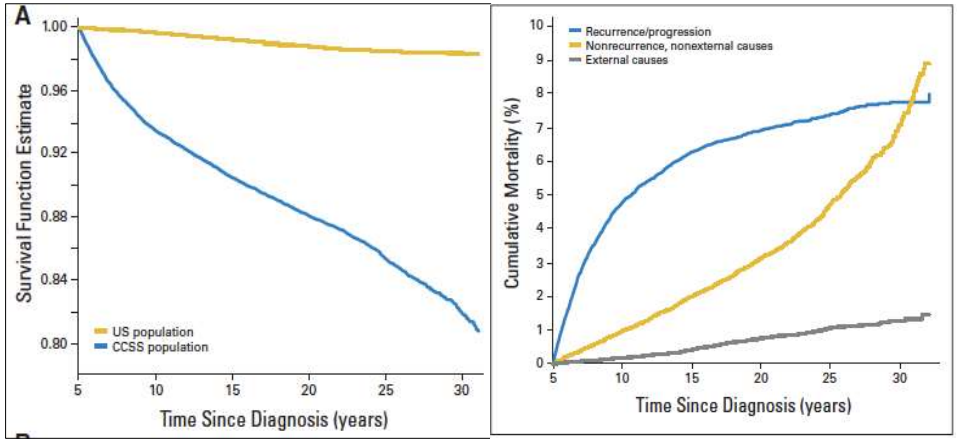
“Life after cancer is complex and no doubt varies for each and every one of us. My experience initially after treatment was euphoric - successfully completing treatment and being able to physically experience normalcy for the first time in years left me feeling so grateful for life. However, this feeling didn't last forever, and as years went on in this 'new normal' I found it difficult to settle in. I realized that my experiences as a young cancer survivor left me with a perspective on life that seemed to alienate me on the inside.

The biggest struggle for me about life after cancer has been dealing with, and communicating, a life perspective that seems so far from other youth my age (and often times adults as well). Personal concerns beyond health and family are trivial and difficult to grasp - things like money, education, and career. And yet the path we're set on and the expectations we're given post-treatment are grounded in this. A life narrative that seems unfamiliar and irrelevant after spending years fighting for my survival.”

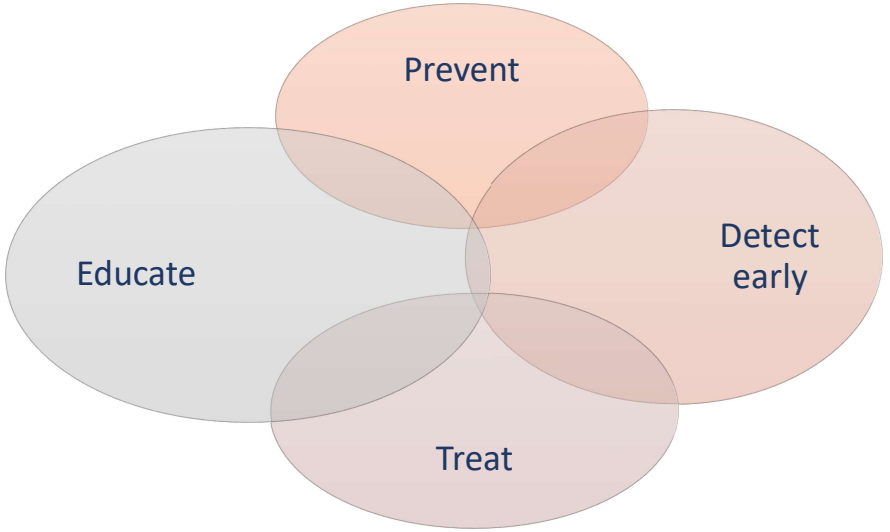
- 6 years since completed treatment for ALL

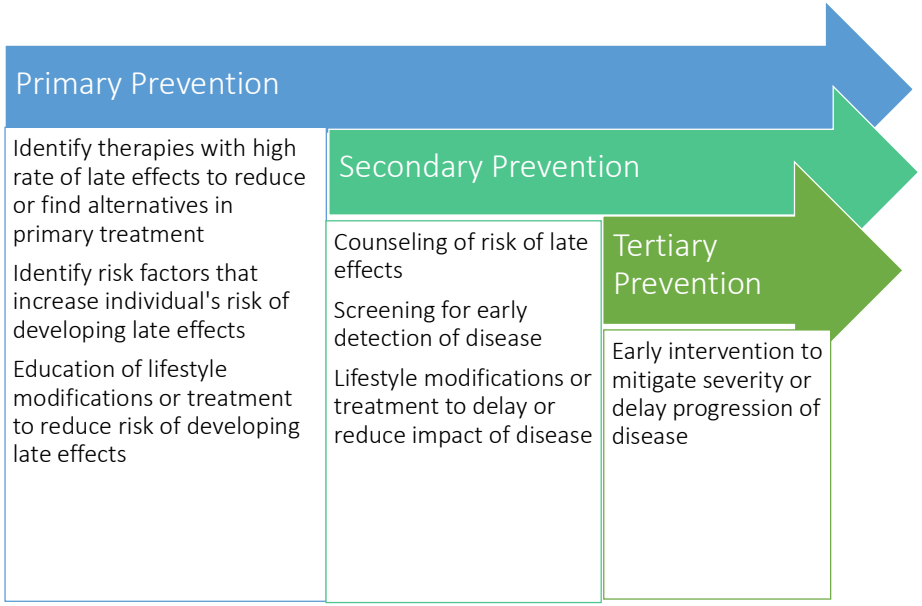
Journey of Survivor – Later years

Higher rates of Mortality



Principles of Long-term Follow-Up Care





CASE 1

ALLison was diagnosed with Acute Lymphoblastic Leukemia at 3 years of age, the most common type of childhood cancer. She is now 8 years old and it has been 3 years since she completed treatment.

Referred to your community office for assessment of behaviour and learning challenges.

Recall 4 factors that may contribute to behavioural and academic challenges in ALL survivors

Standard Risk ALL Therapy

Cycles of intermediate intensity chemotherapy for first 6-8 months; then 2 years of maintenance chemotherapy

Vincristine
Prednisone
Dexamethasone
Doxorubicin 75 mg/m2
Cyclophosphamide 1 g/m2
Peg-Asparaginase

6-mercaptopurine
6-thioguanine
Methotrexate
Cytarabine
Intrathecal methotrexate
Intrathecal cytarabine

ALLison

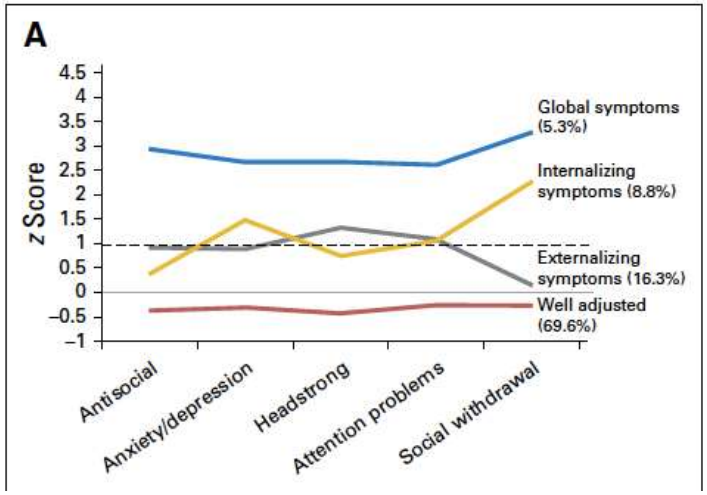
- Healthy
  - No medical issues
  - Grade 3
  - Swimming & gymnastics

Anxious

Extremely shy

Hates school

Neurocognitive & Mental Health



4 factors that may contribute to behavioural and academic challenges in ALL survivors

Psychological impact of treatment	PTSD, Anxiety, Increased risk Mental Health Disorders
Acute illness, missed school & social interactions	Developmental Delay; Lack of peer relationships
Intrathecal chemotherapy	Learning disability (math) ADHD
CNS Radiation therapy	Cognitive impairment Poor working memory

Management

Referral for assessments:

- Developmental / Neurocognitive disorder
- ADHD assessment
- Neuropsychology assessment
- Psychoeducational assessment
- Psychiatry

School supports

- IEP, EA, tutoring

Counseling

- Psychology

16 yo girl initially presented with left chest pain after collision in basketball game at age 12 years. Diagnosed with Ewing sarcoma. Underwent treatment with chemotherapy, surgery and radiation. Now 4 years following treatment.

Was seen in emergency with shortness of breath while in PE. CXR and ECG normal. Symptoms resolved with rest. Referral send to your office: “Query asthma”.

Ewing Sarcoma

- Very intensive cycles of chemotherapy for ~1 year
- Surgery: Thoracotomy with tumour resection and 2 partial rib resections
- Radiation to tumour site

Vincristine

Doxorubicin 440 mg/m2

Cyclophosphamide 20.8 g/m2

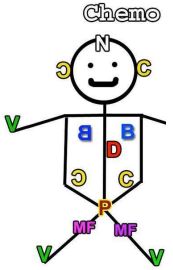
Ifosfamide

Etoposide

Lung

- Restrictive lung disease
  - Thoracotomy
  - Chest wall asymmetry
  - Radiation to lung
  - Radiation to spine with growth restriction

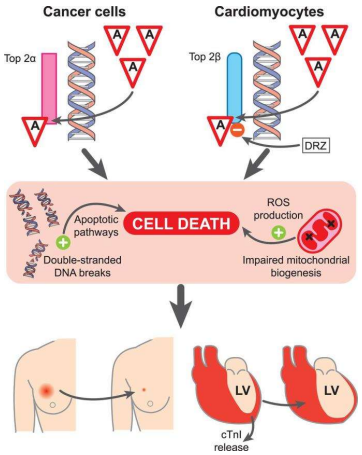
Monitor symptomatically and PFTs

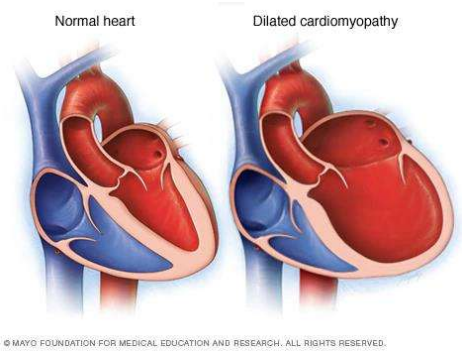


"B" Chemotherapy
Bleomycin, BCNU, Busulfun

Restrictive lung disease
Reduced Diffusion Capacity

Cardiac Toxicity - Anthracyclines





	ALL	Ewing
Doxorubicin (mg/m2)	75	440

Cumulative Effects

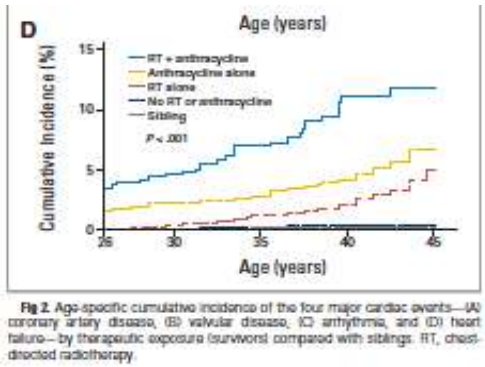
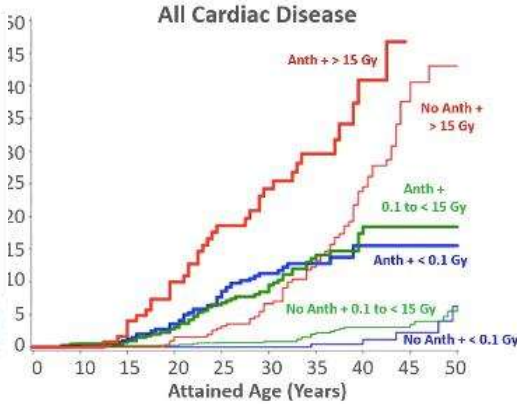


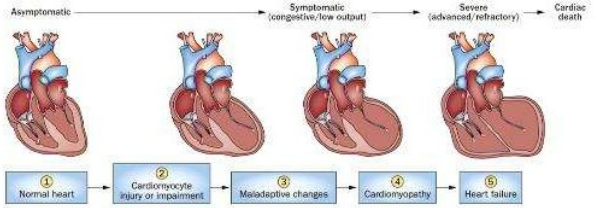
Fig 2. Age-specific cumulative incidence of the four major cardiac events—(A) coronary artery disease, (B) valvular disease, (C) arrhythmia, and (D) heart failure—by therapeutic exposure (survivors) compared with siblings. RT, chest-directed radiotherapy.

Armstrong et al JCO 2013. Pediatric CCSS



Haddy, et al *Circulation* 2016

Prevention



Lipshultz, et al *Nat Rev Clin Oncol* 2013

	PRIMORDIAL Prevention	PRIMARY Prevention	SECONDARY Prevention	TERTIARY Prevention
Definition [a]	An intervention aiming to prevent the development of disease risk factors	An intervention implemented before evidence of disease/injury	An intervention implemented after disease onset, but asymptomatic	An intervention implemented after established disease
Intent [a]	Eliminate causative risk factors (risk avoidance)	Mitigate causative risk factors (risk reduction)	Early identification (screening) and treatment	Prevent progression/sequelae
Cardiac Example [b]	**Risk-adapted therapy to *eliminate* radiation**	Dexrazoxane Cardioprotectant	**Screening echos or biomarkers for asymptomatic left ventricular dysfunction**	**Treat cardiomyopathy with ACE-I's and/or β-blockers**

[a] Adapted from: Centers for Disease Control and Prevention: A Framework for Assessing the Effe… MMWR. 1992;41(RR-3):001.

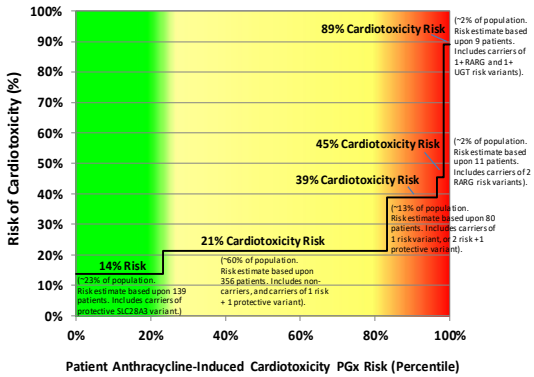
[b] Adapted from Armenian and Ehrhardt, *J Clin Oncol* 2018

Carvedilol Study

Modifiable Factors - Predictive Risk Profile

Genetic factors contribute to individual susceptibility to anthracycline-induced cardiotoxicity.

Recent studies have identified genetic variants associated with toxicity in both children and adults which are involved in the transport or metabolism of anthracyclines and/or its metabolites.

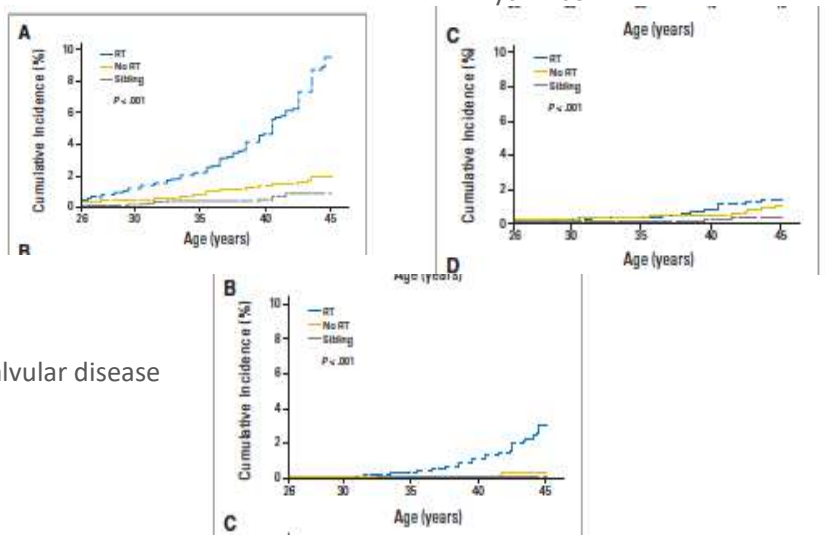


Siemens et al Therapeutic Drug Monitoring 45(3):p 337-344, June 2023.

Impact of Radiation

Ischemic Heart Disease

Arrhythmias



Valvular disease

Cardiac Disease

Non-modifiable	Modifiable	Lifestyle	Social
• Age • Gender • Family history of CVD • Ethnicity • Genetic evidence • Previous history of CVD	• Blood pressure • Total cholesterol • HDL cholesterol • Smoking • Blood sugar/diabetes • BMI • Markers of chronic inflammation	• Smoking • Diet • Exercise • Stress	• Income • Social deprivation • Environment

Chemotherapy
Radiotherapy

Secondary Cardiac Risk Factors

- Deconditioning or limited physical abilities
- Metabolic syndrome
  - Obesity
  - Hypertension
  - Dyslipidemia
  - Impaired fasting glucose
- Iron overload
- Obesity and Sedentary Behaviour

Cardiac Screening

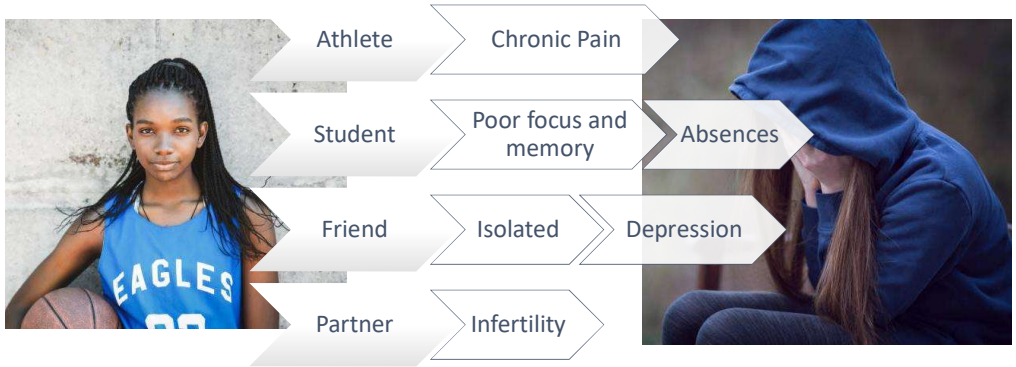
Cardiac Surveillance Guidelines (BC)

Anthracycline Dose*	Radiation Dose**	Recommended Frequency of Echo
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

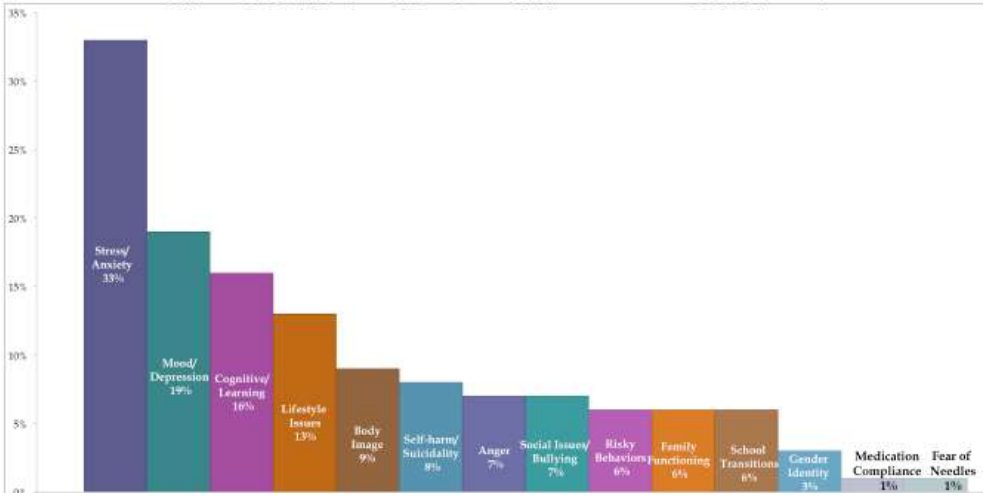
- Protective medication that can be given during treatment to lower risk of damage
- Avoiding cardiac strain
  - Screening for hypertension; counseling on weight lifting
- Screening and counseling on lifestyle measures

Mental Health

Case: Life Interrupted

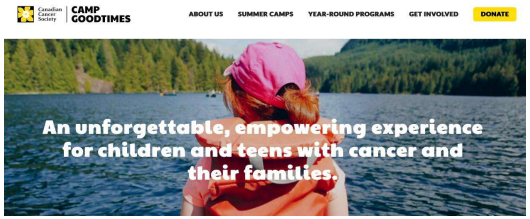


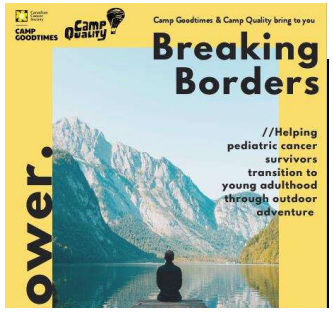
Psychosocial Distress

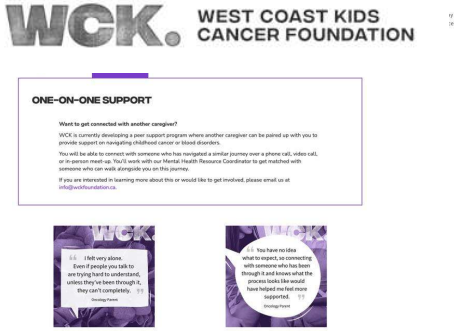


- Psychology screening and counseling support

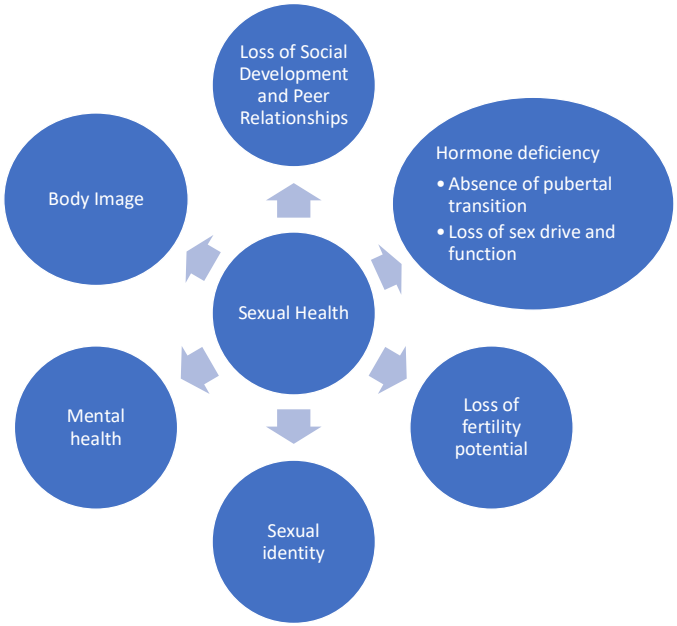
Peer Support





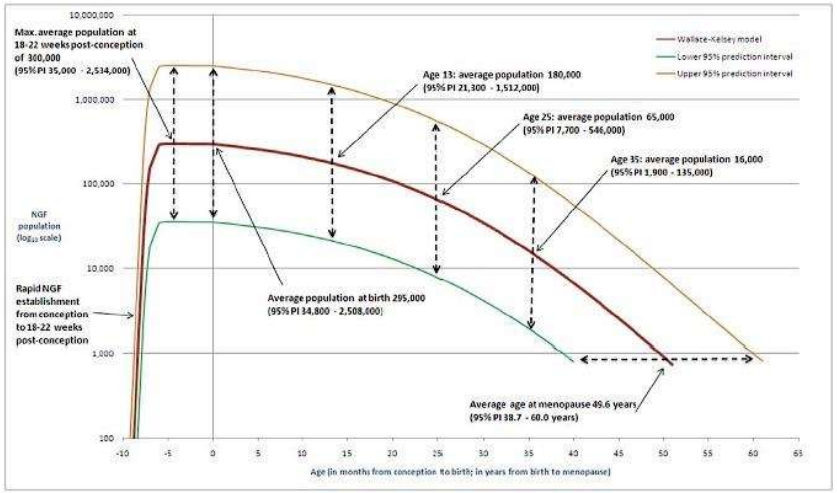


Sexual Health



Gonadotoxicity – Puberty and Fertility

Ovarian Insufficiency



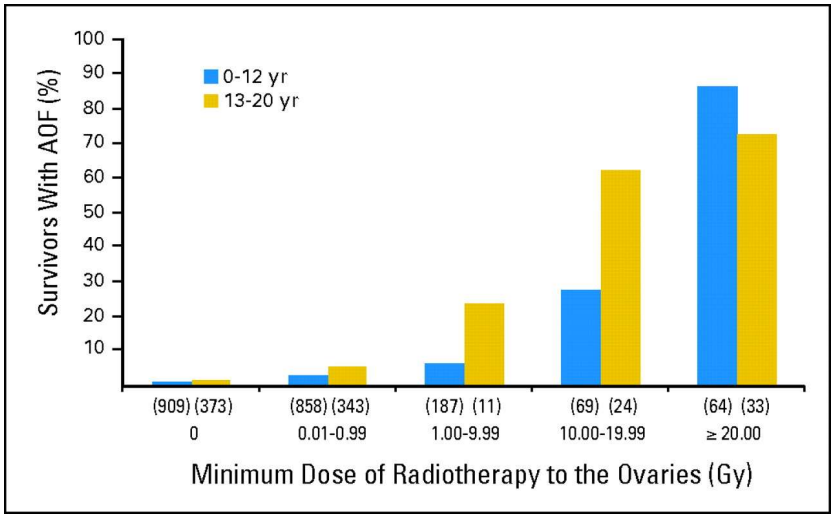
Chemotherapy

CED (mg/m2)	Risk Infertility in Individuals Assigned Male at Birth	Risk infertility in Individuals Assigned Female at Birth
<4000	unlikely	unlikely
4000-8000	40%	30%
8000-20000	60%	50%
>20000	90%	80%

+/- up to 15%

Green et al Pediatr Blood Cancer. 2014; Green JCO 2010

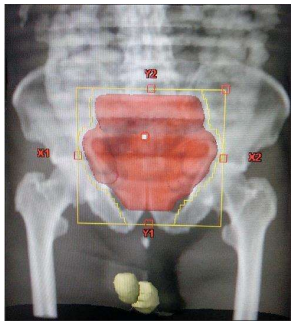
Premature Ovarian Failure



Testicular Radiation

- Spermatogenesis is very sensitive to radiation
  - 0.1Gy can impair spermatogenesis
  - > 0.35Gy can cause permanent azoospermia
  - May have some recovery over a few years

- Leydig cells are more resistant
  - ➢2Gy in prepubertal
  - ➢>3Gy in mature males



Rowley Radiat Res 1974; Shalet J Endocrinol 1989

Screening for gonadal insufficiency

- Pediatrics:
  - Lifelong follow-up care
  - Monitor growth, tanner stage, menses, secondary characteristics
  - Recommend screen of high risk patients with LH, FSH, estradiol or testosterone starting at age 12y

Case 3 Baby Medu Loblastoma

- Originally presented at age 23 months with vomiting and lethargy. Diagnosed with Medulloblastoma. Treated with surgical resection, followed by intensive chemotherapy with autologous stem cell transplant
- Relapsed at age 3.5 years. Underwent additional surgery, followed by craniospinal radiation and further chemotherapy

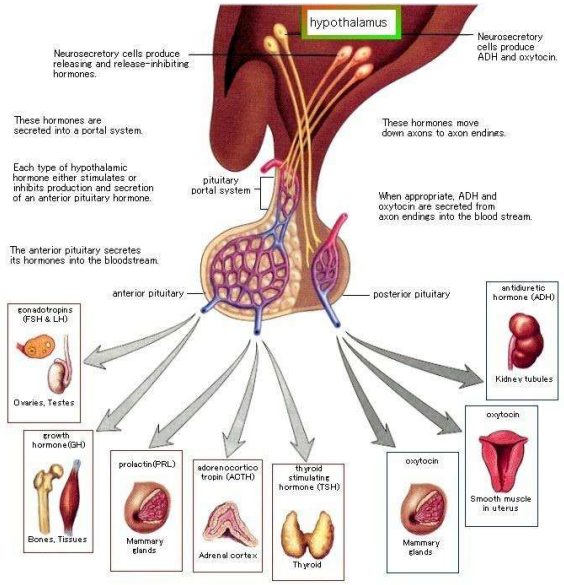
Referred to office for
“complex health needs due to late effects of craniospinal irradiation”

Neurologic and Neurocognitive Impact

- Developmental delay
- Lower IQ
- Learning Disability
- Mental Health
- Seizures

- Lower reports about quality of life
- Lower educational achievements
- Lower rates of employment
- Lower rates of successful relationships

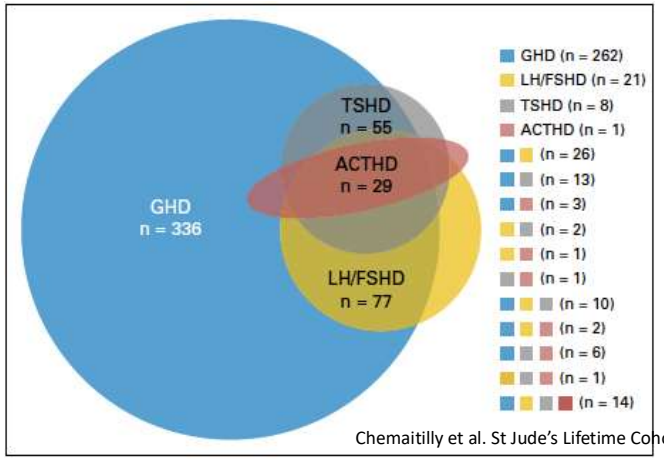
Endocrine



Cranial RT & Central HP axis deficiencies

- Timing: Months to Years after exposure
- Prevalence:
  - 1 deficiency = 51% of survivors
  - Multiple deficiencies 11%

Prevalence of Central Endocrinopathies after Cranial RT



Chemaitilly et al. St Jude's Lifetime Cohort Study. JCO 2015

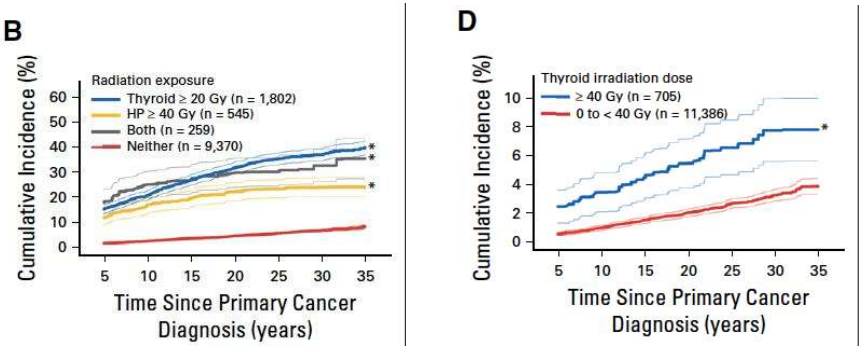
Dose Dependent

Mean dose to hypothalamus	Time to development of GH deficiency	Effect on LH and FSH	TSH deficiency	ACTH deficiency	
					Prolactin Deficiency
10–15 Gy	Unknown				
15–20 Gy	60 months	Precocious puberty, in girls more than in boys	Rare	Rare	
25–30 Gy	36 months	Precocious puberty, equally in girls and boys			
30 Gy		LH and FSH deficiency possible CRI doses >30 Gy	Possible	Possible in brain tumour survivors especially, or in patients with other pituitary hormone deficiencies	Possible
42–60 Gy					
>60 Gy	12 months		Very likely		Likely

Crowne Lancet Diabetes Endocrine 2015

Thyroid

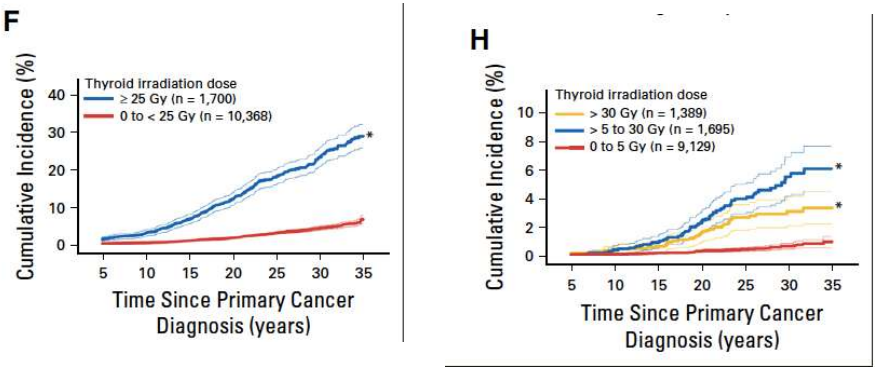
- One of the most common late effects in survivors
- Screening recommended
  - Yearly TSH and free T4



Hypothyroidism Hyperthyroidism

Moustafi-Moab CCSS JCO 2016

Thyroid nodules Thyroid cancer



Moustafi-Moab CCSS JCO 2016

Second Cancers

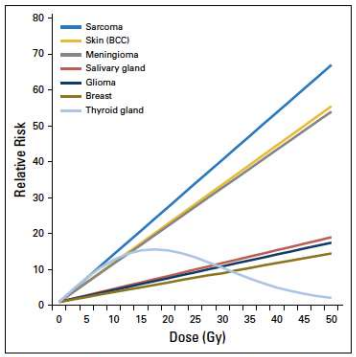


Fig 2. Fitted radiation dose response by type of second cancer, on the basis of previously published reports from the Childhood Cancer Survivor Study. Reprinted with permission.[15]

Chemotherapy (Cyclophosphamide, Doxorubicin, Etoposide)

Secondary Leukemia

Radiation

Both benign and malignant

- Skin cancer
- Bone and soft tissue cancers
- Brain tumours
- Thyroid cancer
- Breast cancer

Screening recommendations

Eg breast MRI and mammogram at later of 8 years after treatment or age 25y

Turcotte et al JCO 2018

Bone Growth

- Short stature secondary to poor spinal growth
- Scoliosis or kyphosis
- Low bone density

Hearing loss

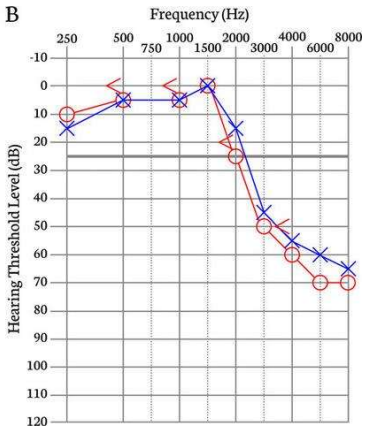
- Impact speech development
- Social interactions

- Prediction tools based on genetics to know who is most susceptible to cisplatin
- Protective agents (Sodium Thiosulfate)

- Screening recommendations based on age and exposure
- Hearing aids, school supports

Hearing loss from Platin chemotherapies

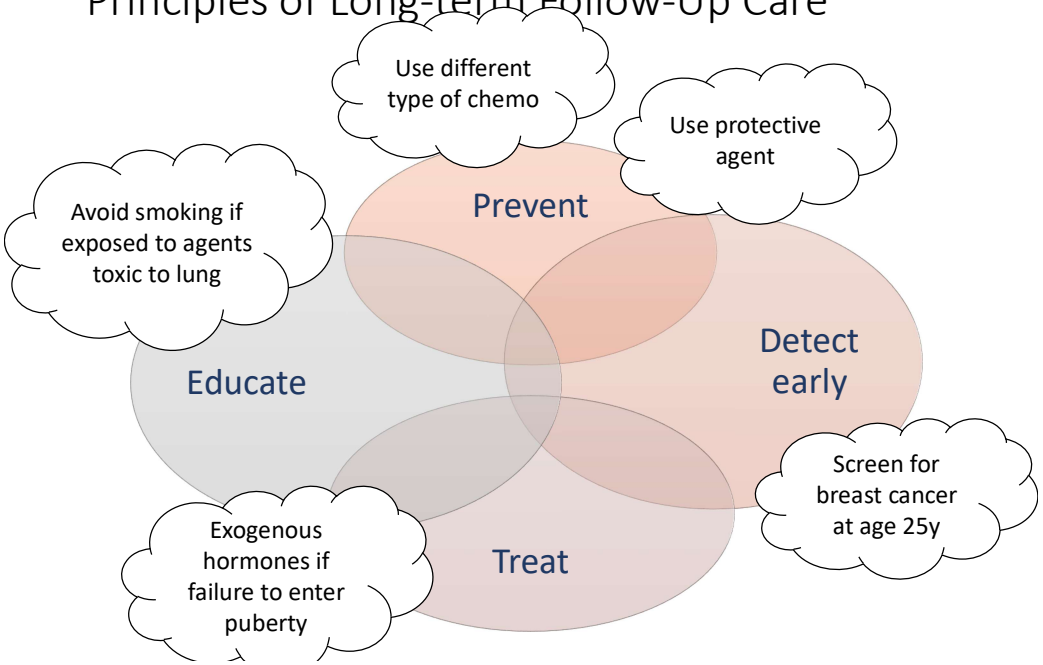
Almost half of patients will develop severe hearing loss



Other risks of cranial/spinal radiation

- Cataracts
- Abnormal dentition
- Metabolic syndrome
- Alopecia and dermatologic changes
- Vascular disease
  - Stroke
  - Ischemic heart disease
- Cardiac
- Lung
- Esophageal stricutres
- Bladder strictures
- Gonadotoxicity

Principles of Long-term Follow-Up Care



Resources

- Treatment summary with patient-specific risk evaluation & surveillance and screening recommendations
- BC LTFU guidelines

  http://www.bcchildrens.ca/health-professionals/clinical-resources/oncology#LTFU--Guidelines
- COG LTFU guidelines

  http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf
- Health links

  http://www.survivorshipguidelines.org/

BC LTFU Guidelines

Ewing Sarcoma
Pediatric Surveillance & Follow-up Guidelines

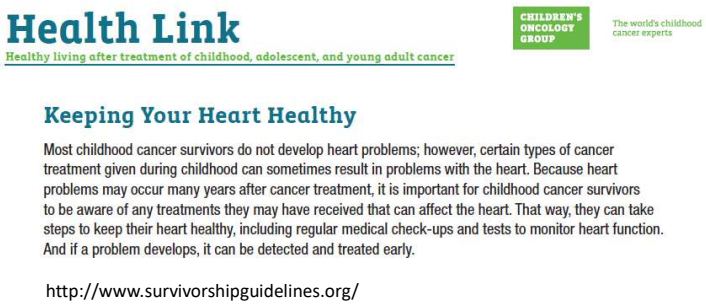
	Months from end of therapy	Date	Location	H&P	CBC	Chem	Imaging of Primary	CXR	Urine tests	GFR	ECG & ECHO*	PFTs	Ortho / Physio	LH, FSH, Test, Est
	0			End of treatment evaluations (per protocol)										
Early Follow-up Clinic	3			+	+	+	+	+	+					
	6			+	+		+	+					+	
	9			+			+	+						
	12			+	+	+	+	+	+		+	+	+	
	15			+			+	+						
	18			+			+	+						
	21			+			+	+						
	24			+	+	+	+	+	+				+	
LTFU clinic	30			+			+	+						
	36			+	+		+	+			+		+	
	42			+			+	+						
	48			+	+		+	+	+				+	
	54			+			+	+						
	60			+	+	+	+	+			+			
	Notes					Lytes, Ca, Mg, PO4, Cr, urea, LFTs			U/A, urine Prot:Cr & Alb:Cr ratio	If renal RT. Repeat Q2y	*Insert added frequency based on cardiac guidelines (see over)	If lung RT or surgery. Repeat Q2y if abN		Baseline age 13y if CED <4 g/m². Baseline age 11 y & rpt Q1y if CED ≥4

COG LTFU Guidelines

RADIATION — **POTENTIAL IMPACT TO NECK/THYROID (CONT)**

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
68	**Head/Brain** **Neck** **Spine (cervical, whole)** **TBI**	**Hypothyroidism**	**HISTORY** **Fatigue** **Weight gain** **Cold intolerance** **Constipation** **Dry skin** **Brittle hair** **Depressed mood** Yearly, consider more frequent screening during periods of rapid growth **PHYSICAL** **Height** **Weight** **Hair** **Skin** **Thyroid exam** Yearly, consider more frequent screening during periods of rapid growth **SCREENING** **TSH** **Free T4** Yearly, consider more frequent screening during periods of rapid growth	**HEALTH LINKS** **Thyroid Problems** **COUNSELING** For females, thyroid levels prior to attempting pregnancy and periodically throughout pregnancy. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Endocrine consultation for thyroid hormone replacement. **SYSTEM = Endocrine/Metabolic** **SCORE = 1**

Education & counseling



Health Link

Healthy living after treatment of childhood, adolescent, and young adult cancer

CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Keeping Your Heart Healthy

Most childhood cancer survivors do not develop heart problems; however, certain types of cancer treatment given during childhood can sometimes result in problems with the heart. Because heart problems may occur many years after cancer treatment, it is important for childhood cancer survivors to be aware of any treatments they may have received that can affect the heart. That way, they can take steps to keep their heart healthy, including regular medical check-ups and tests to monitor heart function. And if a problem develops, it can be detected and treated early.

http://www.survivorshipguidelines.org/

International Guideline Harmonization Group

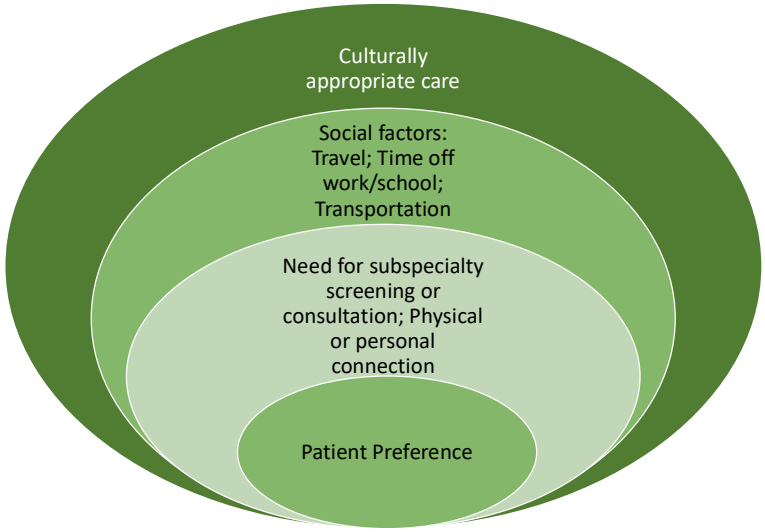
for Late Effects of Childhood Cancer

- breast cancer,
- cardiomyopathy,
- premature ovarian insufficiency,
- male gonadotoxicity,
- thryoid cancer,
- ototoxicity
- fatigue surveillance,
- obstetric care
- fertility preservation.

https://www.ighg.org/guidelines/topics/

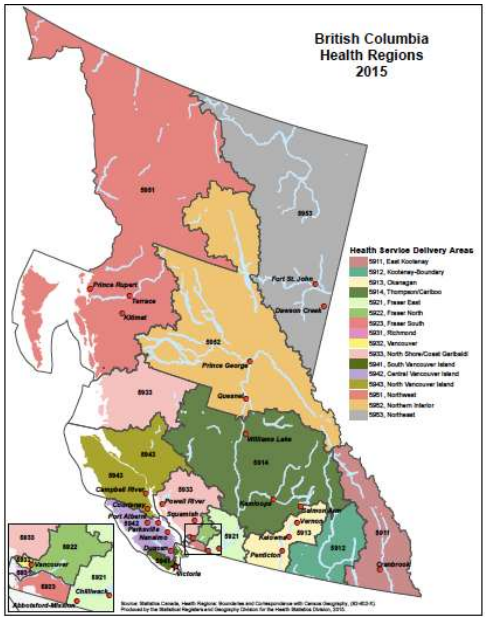
Changing with the Times: Lessons learned during the pandemic

Individualized approach to model of care



Access to care

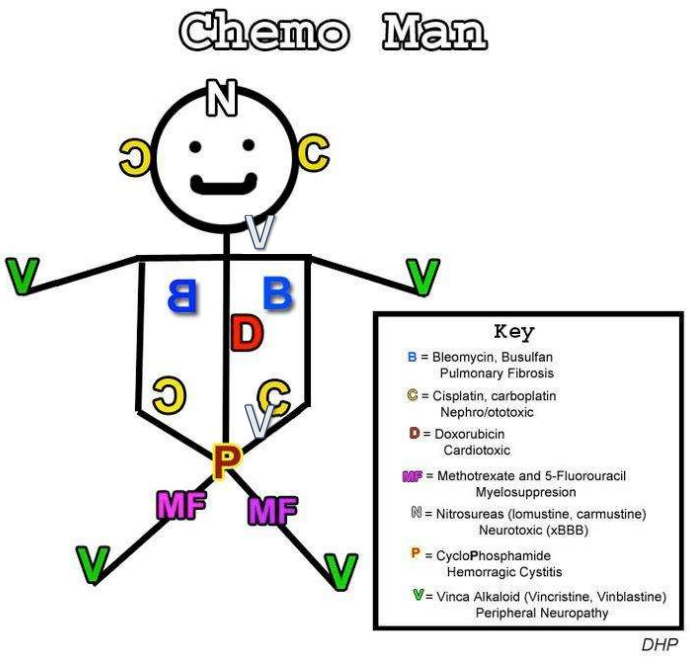
- Community Outreach Clinics
  - Kamloops
  - Kelowna
  - Prince George
- Partnership with Local Pediatricians and Providers
- Virtual Care



Cancer as Chronic Illness

Survival rates are good but patients can have a significant health burden as a consequence of their disease and treatment

Always learning and improving our care to increase rates of cure but also to improve quality of life in survivors



Late Effects of Chemotherapy

Chemotherapy	Special Late Effects	
Cyclophosphamide	Cystitis Infertility >7.5 g/m2 Secondary malignancy (bladder, AML)	Yearly Hx and Px Yearly urinalysis Yearly CBC until 10 y post
Ifosfamide	Tubulopathies Infertility >60 g/m2	Yearly BP Yearly urinalysis Lytes prn
Etoposide	Secondary AML (Early - < 3 y post)	Yearly CBC until 10 y post
Cisplatin/Carboplatin	Ototoxicity Nephrotoxicity	Baseline hearing test & early if abN. Yearly BP Yearly urinalysis Lytes prn

Chemotherapy	Special Late Effects	
Cytarabine (High dose IV)	Neurocog deficits (LD, lower IQ, behaviour) Leukoencephalopathy Cerebellar dysfunction	Yearly Hx and Px Neuropsych testing MRI if needed
BCNU/CCNU	Pulmonary fibrosis Secondary AML	Yearly Hx and Px PFT – baseline and as indicated Yearly CBC until 10 y post
Dactinomycin	None	
Steroids	Reduced bone density AVN Cataracts	Yearly Hx and Px

Chemotherapy	Special Late Effects	
Vincristine	None (can have chronic issues from acute effects)	
Bleomycin	Pulmonary fibrosis Risk of ARDS or lung injury with reactive oxygen species	Yearly Hx and Px PFT – baseline and as indicated
Doxorubin/ Daunorubicin	Cardiomyopathy (CHF, dilated CM) Valvular disease Secondary AML	Yearly hx and px ECHO per risk
Methothrexate	Cognitive impairment ADHD Leukoencephalopathy	Neuropsych MRI if needed
Asparaginase	None	