The Struggles of Childhood Cancer Survivors

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Pediatric Hematology/Oncology

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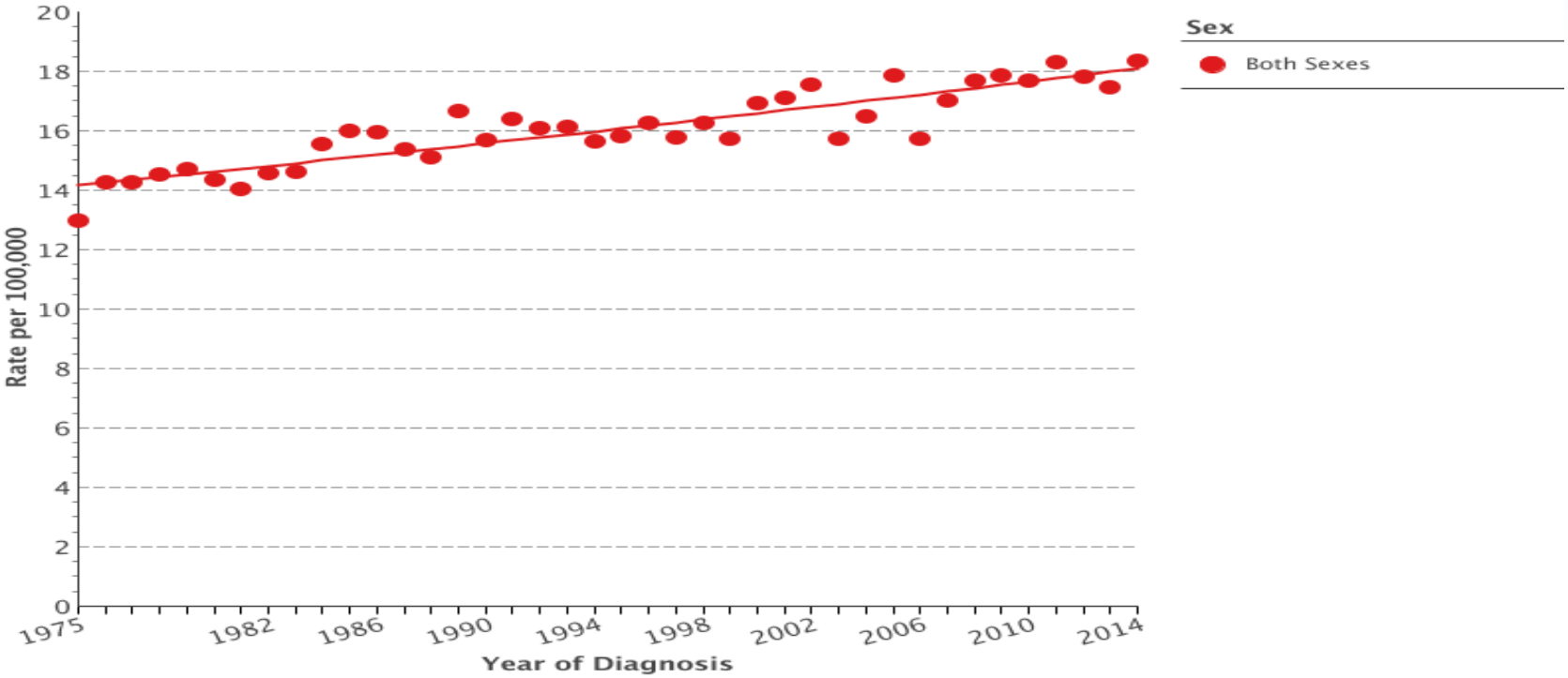
Disclosures

- None

Objectives

- Epidemiology of the most common childhood cancers
- Long term side effects associated with childhood cancers treatments and how to screen for, diagnose and treat these outcomes
- Discuss newer treatment modalities for childhood cancers that have had an impact on improved survival rates in the last 10 years
- Identify areas of ongoing research that are most promising to improve future survival rates and decrease the risks of long-term adverse sequelae in childhood cancer survivors

Introduction



SEER 9 areas [http://seer.cancer.gov/registries/terms.html] (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
The Annual Percent Change (APC) estimates were calculated from the underlying rates using the Joinpoint Trend Analysis Software [http://surveillance.cancer.gov/joinpoint], Version 4.4, January 2017, National Cancer Institute.
The APC's direction is "rising" when the entire 95% confidence interval (C.I.) is above 0, "falling" when the entire 95% C.I. is lower than 0, otherwise, the trend is considered stable.
Cancer sites are defined using the SEER Site Recode ICD-O-3/WHO 2008 Definition [https://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html].
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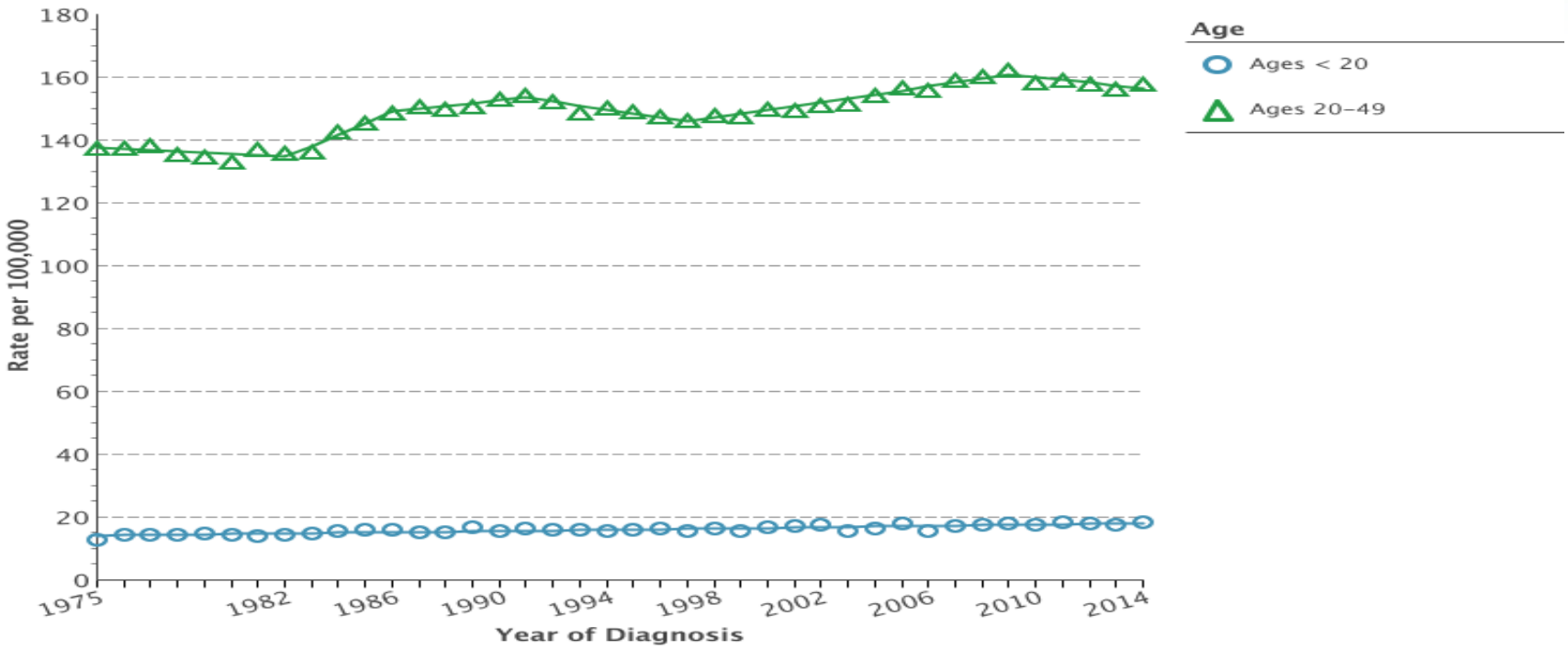
Introduction



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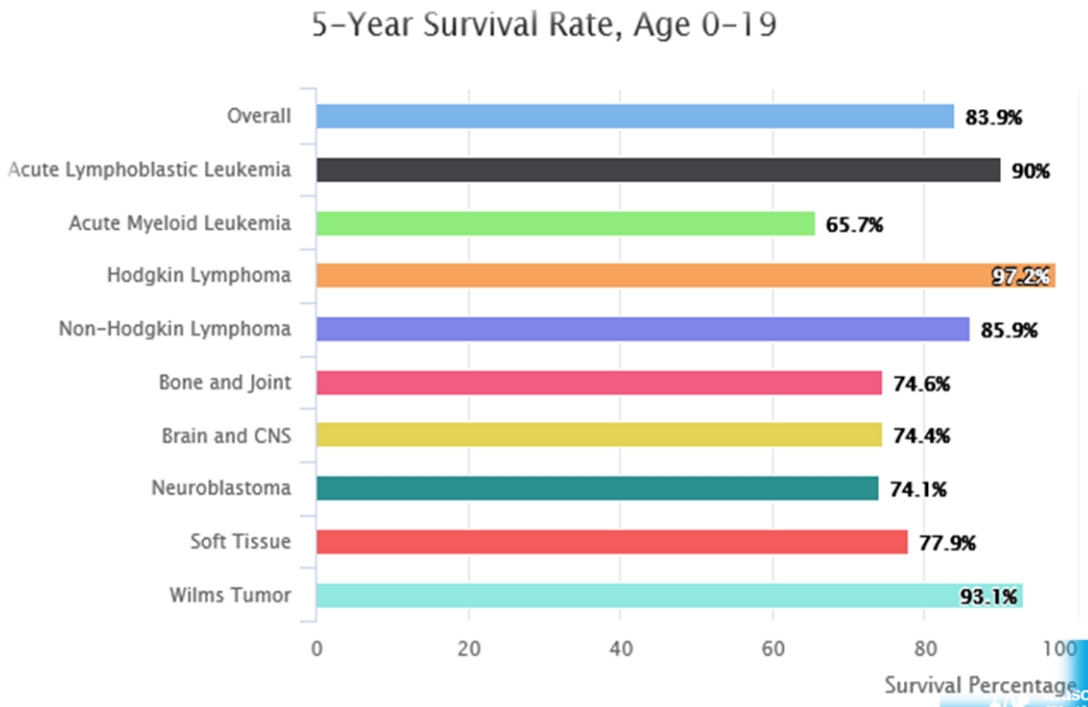
Number of Childhood Cancer Diagnoses Per Year
Total = 15,780, Age 0–19

- Acute Lymphoblastic Leukemia (ALL): 20%
- Brain and Central Nervous System: 18%
- Hodgkin Disease: 8%
- Non-Hodgkin Lymphoma: 7%
- Acute Myeloid Leukemia (AML): 5%
- Neuroblastoma: 5%
- Bone Tumors*: 5%
- Thyroid Carcinoma: 4%
- Wilms / Kidney: 3%
- Germ Cell Tumors: 3%
- Rhabdomyosarcoma: 2%
- Retinoblastoma: 2%
- Melanoma: 2%
- Other: 16%

Source: American Cancer Society, Cancer Facts and Figures (2014)

How far have we come?

- In the last 40 years, the overall survival rate has increased from 10% to 90%
- 12% do not survive
- 60% have significant late effects
- 375,000 adults are survivors of childhood cancers



Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov). SEER 9 area. Based on follow-up of patients into 2012

How did we get here?

- These are the results of cooperative group trials: COG, St Jude and others
- Using multi – modal therapy:
  - Surgery
  - Radiation Therapy
  - Chemotherapy
  - Immunotherapy
  - Bone marrow transplant
- Despite survival near 90%, many experience difficulties related to the specific therapy received and age interruption in growing organs
- New estimates expect 500,000 young adults survivors by 2020
- All in the medical community are likely to have a role in their care

What is the Cost of Cure?

- "Childhood Cancer Survivor study" – followed 24,000 survivors since 1994 (St Jude based), has uncovered multiple associations between treatments and specific late effects
- In 2016, it was published that: ¾ of survivors experience at least one chronic condition 30 years after cancer diagnosis, with 40% of these being life threatening
- Less than one third of young adult survivors report attending survivor focused care
- Risk of late effects increases the further survivors are from therapy, which results in the need for on going awareness and follow up care
- Need for development of dedicated long-term follow-up care programs

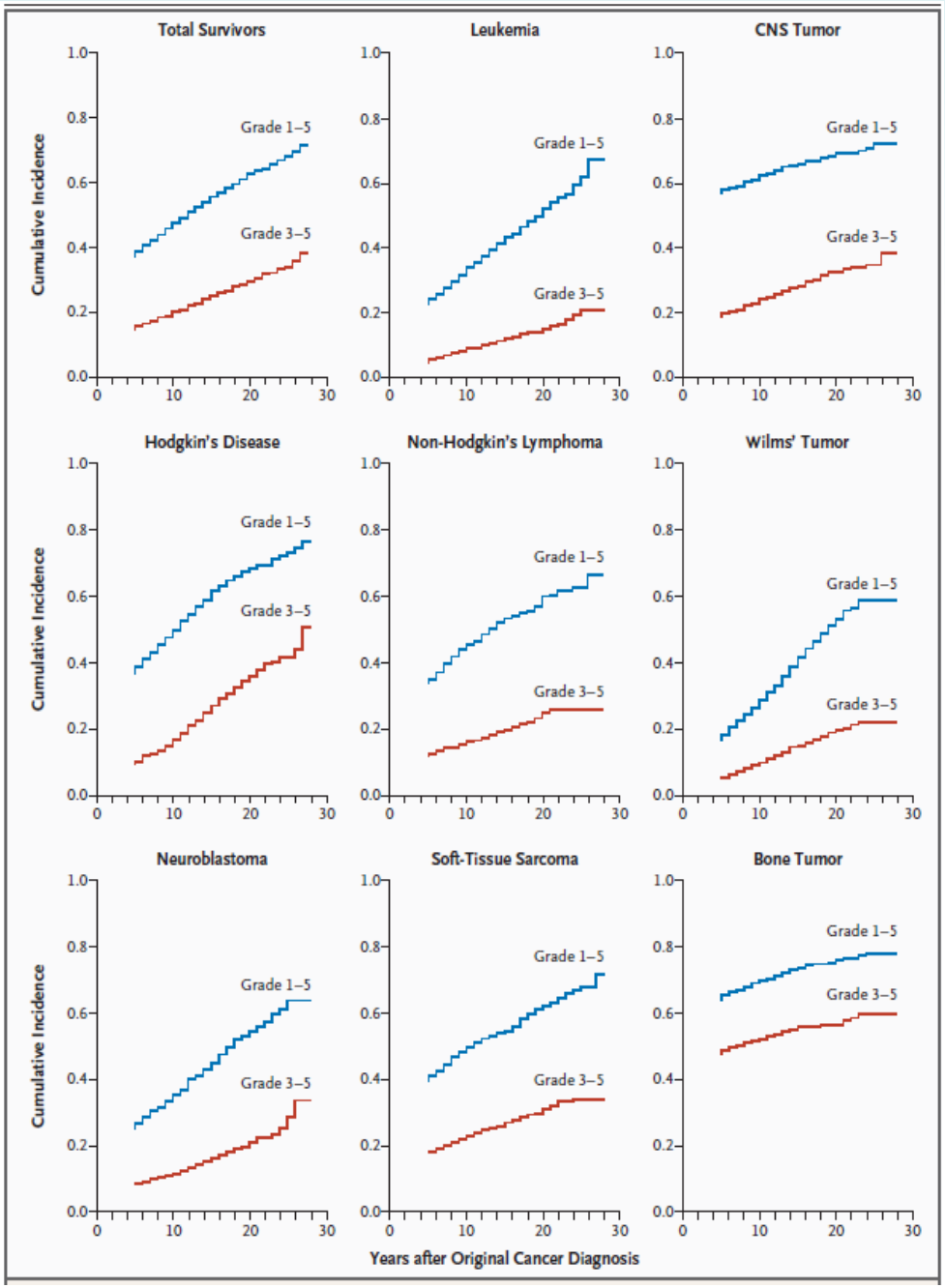


Figure 1. Cumulative Incidence of Chronic Health Conditions among 10,397 Adult Survivors of Pediatric Cancer (1970-1986), According to the Original Diagnosis and the Severity of the Later Condition.

Among the survivors of various types of childhood cancer, the severity of subsequent health conditions was scored according to the Common Terminology Criteria for Adverse Events (version 3) as either mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). For the total survivor cohort, the curves showing the cumulative incidence of the two outcomes by grade are truncated at 28 years, even though the text provides data up to 30 years after the original cancer diagnosis. This was done for consistency with the panels showing data for groups of patients with certain types of cancer, in which smaller samples yielded data that were not as robust at 30 years as they were at 28 years.

Oeffinger KC et al. N Engl J Med 2006;355:1572-82.

Late mortality

- Recent study compared the US cohort (28,248) to the British cohort (18,226) treated between 1970-1999
- 6000 deaths in total with UK experiencing more progression/recurrence deaths
- Cumulative all-cause mortality at 10 years from diagnosis was lower for the US cohort (4.8% vs 6.9%)

- PCSF study included 77,423 survivors with SMR of 9.89 and AER of 6.47/1000 person years
- Primary cause of death was primary malignancy – 55.8%
- Mortality rates reached a lower point between 20-30 years from diagnosis and increased from there to the end of follow-up
- 50-54 years from diagnosis, SMR was 3.75 with AER was 20.47/1000 person years

Fidler-Benaurdia et al. Comparing Late mortality risk among childhood cancer survivors: a report from the childhood cancer survivors study and British childhood cancer survivor study. Jun 2019 NASLCCC
Byrne et al. Very late excess mortality in older adults from the Pancaresurfup study of 77,423 five year survivors of childhood and adolescent cancer. Jun 2019 NASLCCC

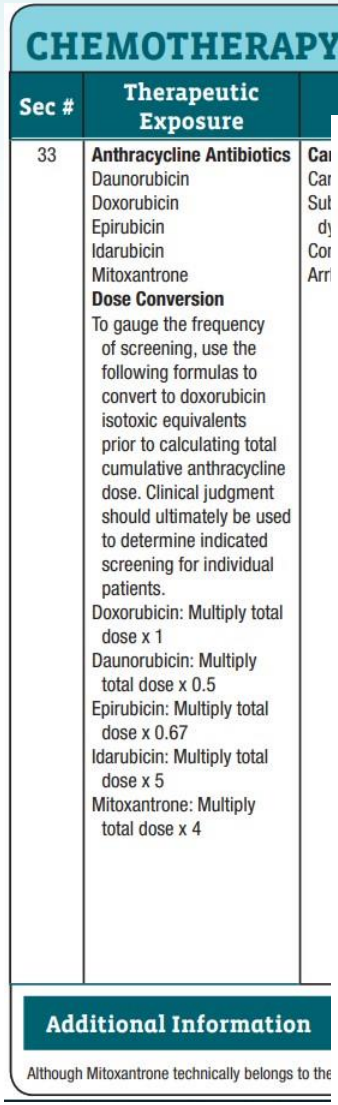
Pioneers

Dr Anna Meadows

Wendy Hobbie, CRPN

- In early 80's at CHOP, they developed an organized program and published guidelines to help focus on many issues that survivors were facing
- In 1995, with more survivors and emerging needs in our practice at MUSC, we began the FACT program with guidance from the CHOP team
- Gradually this type of program increased across the globe
- By early 2000, Children Oncology Group worked on general guidelines

Survivorship Guidelines



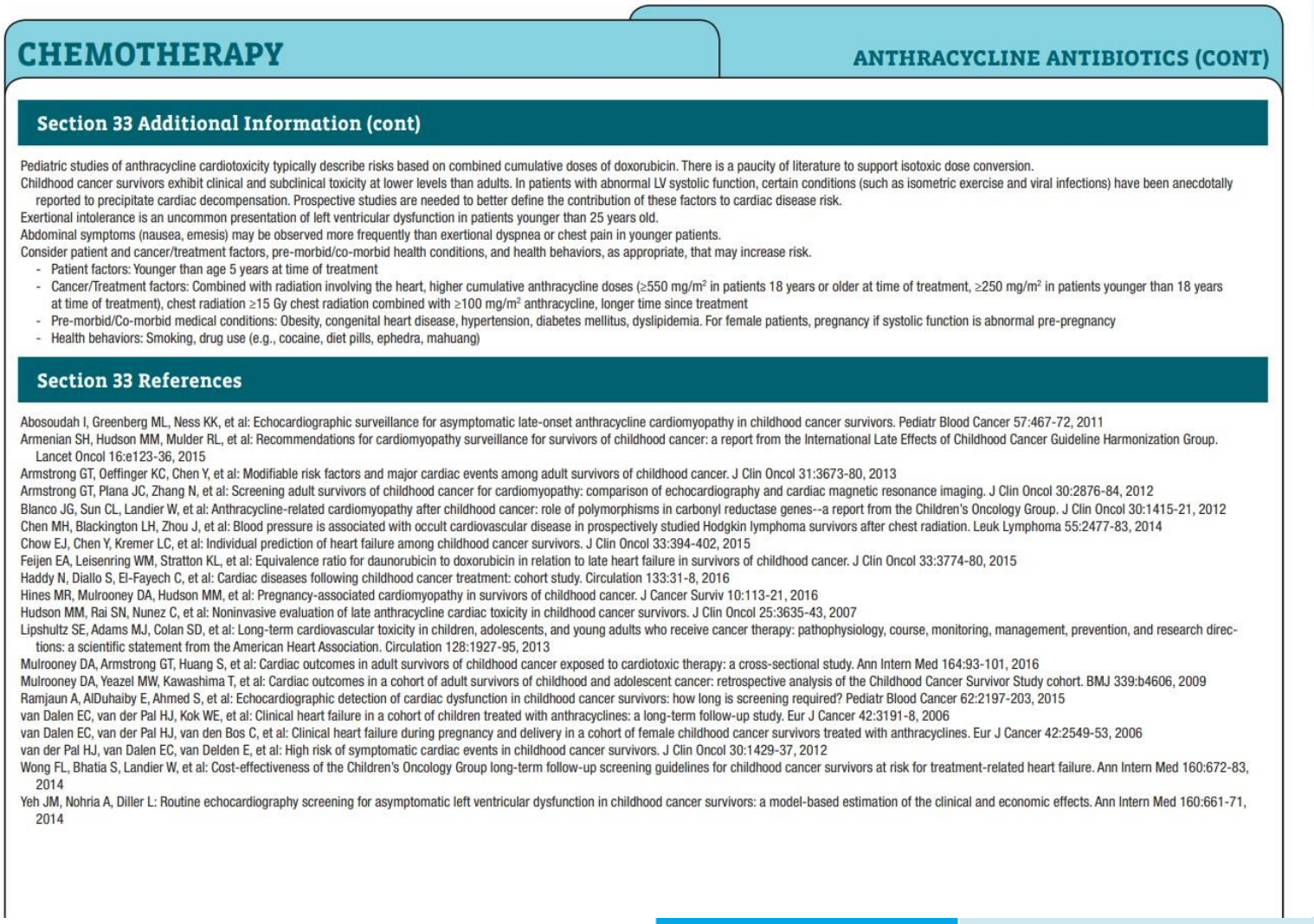
CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Sec #	Therapeutic Exposure	Potential	Periodic Evaluation	Health Counseling/
33	**Anthracycline Antibiotics** Daunorubicin Doxorubicin Epirubicin Idarubicin Mitoxantrone **Dose Conversion** To gauge the frequency of screening, use the following formulas to convert to doxorubicin isotoxic equivalents prior to calculating total cumulative anthracycline dose. Clinical judgment should ultimately be used to determine indicated screening for individual patients. Doxorubicin: Multiply total dose x 1 Daunorubicin: Multiply total dose x 0.5 Epirubicin: Multiply total dose x 0.67 Idarubicin: Multiply total dose x 5 Mitoxantrone: Multiply total dose x 4	Ca Ca Su dy Co Arr		

Additional Information

Although Mitoxantrone technically belongs to the



CHEMOTHERAPY

ANTHRACYCLINE ANTIBIOTICS (CONT)

Section 33 Additional Information (cont)

Pediatric studies of anthracycline cardiotoxicity typically describe risks based on combined cumulative doses of doxorubicin. There is a paucity of literature to support isotoxic dose conversion.

Childhood cancer survivors exhibit clinical and subclinical toxicity at lower levels than adults. In patients with abnormal LV systolic function, certain conditions (such as isometric exercise and viral infections) have been anecdotally reported to precipitate cardiac decompensation. Prospective studies are needed to better define the contribution of these factors to cardiac disease risk.

Exertional intolerance is an uncommon presentation of left ventricular dysfunction in patients younger than 25 years old.

Abdominal symptoms (nausea, emesis) may be observed more frequently than exertional dyspnea or chest pain in younger patients.

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Younger than age 5 years at time of treatment
- Cancer/Treatment factors: Combined with radiation involving the heart, higher cumulative anthracycline doses (≥550 mg/m^2 in patients 18 years or older at time of treatment, ≥250 mg/m^2 in patients younger than 18 years at time of treatment), chest radiation ≥15 Gy chest radiation combined with ≥100 mg/m^2 anthracycline, longer time since treatment
- Pre-morbid/Co-morbid medical conditions: Obesity, congenital heart disease, hypertension, diabetes mellitus, dyslipidemia. For female patients, pregnancy if systolic function is abnormal pre-pregnancy
- Health behaviors: Smoking, drug use (e.g., cocaine, diet pills, ephedra, mahuang)

Section 33 References

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COG, Long-Term Follow Up Guidelines for survivors of childhood, adolescent and young adult cancer, Oct 2018

Survivorship 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**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.

- Patient factors: Female sex
- Cancer/Treatment factors: Radiation dose ≥10 Gy (especially radiation dose ≥20 Gy), thyroid gland directly in radiation field, TBI

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COG, Long-Term Follow Up Guidelines for survivors of childhood, adolescent and young adult cancer, Oct 2018

Long term complications

- Can be caused by:
    - Chemotherapy
    - Immunotherapy
    - Bone marrow transplant (BMT)
    - Radiation therapy: localize radiation therapy, total body radiation(TBI)
    - Surgery
- Some of the side effects are yet to be discovered
- Can present at any point in time during the patient's life
- It takes 20-30 years from exposure to discover these side effects, so new therapies are still being monitored for side effects
- Goal of cancer treatment is to reduce long term side effects with no change or improvement in survival

Long term complications

- Psychological
  - Neurologic
    - Endocrine
      - Fertility
        - Cardiac
          - Pulmonary
            - Secondary malignancy
- Dermatologic
  - Ophthalmologic
    - Hepatic
      - Renal
        - Musculoskeletal
          - Dental

Psychological Complications

- Can be seen with any type of cancers
- One of the most common complications
- Can present with:
  - Depression
  - Anxiety
  - PTSD
- Using screening tools or having a psychologist integrated in the clinic
- Need for counseling and medical interventions
- Sometimes the resources in the community are limited

Neurologic and Educational Complications

- Causing agents: chemotherapy (IT chemotherapy, high dose methotrexate), cranial radiation, TBI, location of the tumor
- Types: acute lymphoblastic leukemia, osteosarcoma, brain tumors, bone marrow transplant
- Cisplatin and carboplatin can cause hearing loss in addition to tumor location and radiation therapy
- Can present with:
  - ADHD
  - Hearing loss
  - Learning disabilities – impairment in processing speed and executive function
  - Cerebrovascular disease
  - Fine motor or gross motor deficits

Neurologic and Educational Complications

- Ness et al. in 2008 – looked for functional limitations in 7147 adult survivors and found that 14% reported impairment in executive functioning

- A review article by Cheung et al. summarized that even with the omission of CRT, long-term ALL survivors who are treated with contemporary chemotherapy protocols are at risk of experiencing neurocognitive deficits

- Cheung et al. in 2018 – looked at 235 samples of CSF from children with ALL at diagnosis and after IT chemotherapy and found evidence of glial injury present at diagnosis and neuronal injury after administration of IT chemotherapy

Ness KK, et al. Arch Phys Med Rehabil 89:128-136, 2008
Yin Ting Cheung, Kevin R. Krull, Neuroscience and Biobehavioral Reviews 53 (2015) 108–120
Yin Ting Cheung et all, JAMA Oncology Published online March 29, 2018

Neurologic and Educational Complications

- Periodic evaluations with neurocognitive testing
- Help in some cases with future educational choices
- Audiogram
- Physical therapy and occupational therapy
- Education about signs and symptoms of stroke
- Monitoring life style habits

Ototoxicity

- Dose of chemotherapy influences the risk of ototoxicity
- Patients who received carboplatin in non-myeloablative doses do not appear to be at risk for clinically significant ototoxicity
- Infants who received carboplatin in non-myeloablative doses may have hearing loss after treatment
- Hearing evaluation is done during treatment and also during survivorship clinic
- Use of special accommodations may be needed, avoidance of high noise areas, hearing aids

Gilmer et al. J Clin Oncol.2005;Dec 1 23(34):8588-8596
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Endocrine Complications

- Caused by radiation therapy, chemotherapy, tumor location
- Types: brain tumors, sarcomas, leukemias, lymphomas, bone marrow transplant
- Include:
  - Obesity
  - Growth hormone deficiency – primarily due to RT
  - Low bone density/vitamin D deficiency
  - Panhypopituitarism – primarily due to RT
  - Gonadal dysfunction
  - Thyroid disorders – primarily due to RT
  - Diabetes mellitus

Obesity

- Causes: prolonged used steroids
- Usually seen in leukemia survivors
- Yearly exam to monitor growth (weight, height and BMI graphs)
- Monitor lipid panel every 2 years
- Discuss importance of healthy habits (eating, activity)

Obesity

BMI distribution before and after therapy.

	Total 1,017	Males 572	Females 445
Pre-treatment			
Underweight - BMI < 5th percentile	54 (5%)	30 (5%)	24 (5%)
Healthy Weight - BMI 5th – 84th percentile	685 (67%)	383 (67%)	302 (68%)
Overweight - BMI 85th – 94th percentile	146 (14%)	83 (15%)	63 (14%)
Obese - BMI >= 95th percentile	132 (13%)	76 (13%)	56 (13%)
At last Maintenance cycle			
Underweight - BMI < 5th percentile	31 (3%)	21 (4%)	10 (2%)
Healthy Weight - BMI 5th – 84th percentile	562 (55%)	318 (56%)	244 (55%)
Overweight - BMI 85th – 94th percentile	189 (19%)	102 (18%)	87 (20%)
Obese - BMI >= 95th percentile	235 (23%)	131 (23%)	104 (23%)

Withycombe et al. Pediatr Blood Cancer. 2015 March ; 62(3): 434–439. doi:10.1002/pbc.25316

Vitamin D deficiency

- Cancer treatments can affect bone mineral density that can cause severe complications in our survivors
- Chemotherapy: steroids, HD MTX, alkylating agents or radiation therapy
- Types: leukemia, lymphoma, osteosarcoma and other sarcoma, neuroblastoma, bone marrow transplant
- Optimizing Vitamin D can prevent some of these complications
- Also weight management, activity level, balanced diet and avoidance of smoking and alcohol may help
- Some studies showed an increase in incidence of vitamin D deficiency in survivors compare with healthy controls

Wasilewski-Masker K et al. PEDIATRICS Volume 121, Number 3, March 2008
Choudhary A et al. Pediatr Blood Cancer 2013;60:1237–1239

Fertility

- Male and female infertility can be caused by tumor location, radiation therapy and chemotherapy-like alkylating agents – cyclophosphamide, ifosfamide, melphalan, thiotepa or heavy metals - carboplatin and cisplatin

- It is related to total cumulative dose

- Types: BMT, brain tumor, ovarian/testicular cancer, sarcomas, less likely in leukemia

- Depending on age and diagnosis, there are methods of fertility preservation that can be done before or during treatment

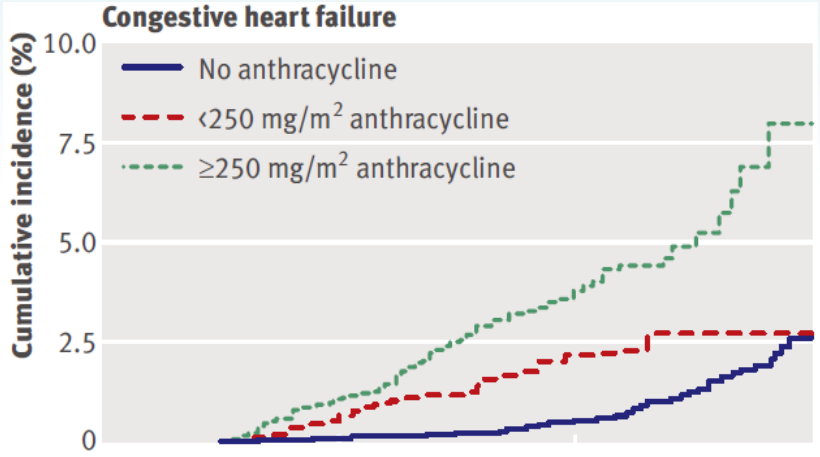
Fertility

- More difficult in children
- Also limited services pretreatment
- Prepubertal children – limited methods
- Post pubertal children – sperm preservation, use of hormonal therapy (progesterone)
- Monitor post-treatment with yearly exam – puberty progression, growth, hormonal levels
- Males can have post treatment sperm analysis to evaluate their fertility potential in addition to hormone levels

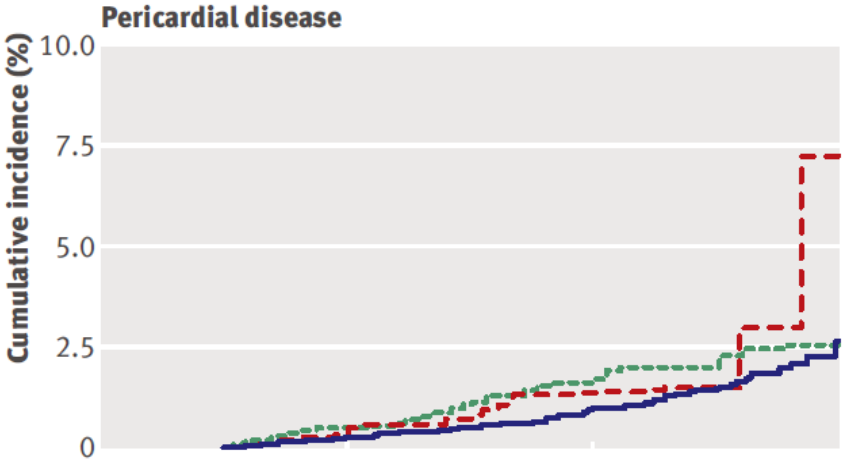
Cardiac Complications

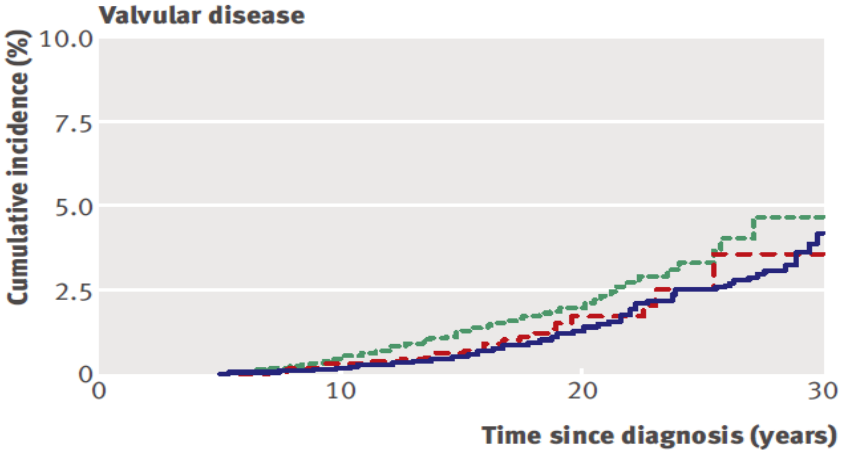
- Caused by radiation therapy, anthracyclines, high doses of alkylating agents
- Are progressive over years and can lead to cardiac dysfunction, coronary artery disease or heart failure
- Monitoring for cardiac complications start at the initiation of chemotherapy
- Associations between anthracyclines and radiation therapy increases the risk of heart disease
- Evaluation for other risk factors: diet, weight, exercise routine, habits, lipid profile

Cardiac Complications



Cumulative incidence of cardiac disorders among childhood cancer survivors by anthracycline dose





Mulrooney et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009;339:b4606

Cardiac Complications

Comparison of studies of pregnancy in childhood cancer survivors

	Bar	Van dalen	Hines	Thompson
Type of study	Prospective	Retrospective	Retrospective	Retrospective
# of patients	37	53	847	58
Mean f/u time	17 years	20.3 years	26.5 years	20 years
Treatment/dose	<500 mg/m2 of anthracycline	267 mg/m2 of anthracycline	57% received anthracycline, 200 mg/m2	97% received anthracycline, 272 mg/m2
Definition of cardiotoxicity	FS <30% by echo	Signs and symptoms	Questionnaires and echoes, SF <28%, EF <50%	EF <50% by echo
Conclusions	Pregnancy did not cause heart failure in those with normal baseline function; pregnancy did not increase risk of cardiotoxicity.	No heart failure occurred. Study was not powered to assess risk.	Pregnancy associated CMP in CCS was low but not insignificant, 1:500 vs. 1:3,000–4,000 in general population.	Subgroups identified with increased risk: 1. younger age at time of cancer diagnosis 2. Longer time from treatment to pregnancy 3. Higher anthracycline dose Pregnancy was an independent risk factor.

f/u, follow up; FS, fractional shortening; SF, shortening fraction; EF, ejection fraction; CMP, cardiomyopathy; CCS, childhood cancer survivor.

Thompson. Pregnancy and Cardiomyopathy After Anthracyclines in Childhood. Frontiers in Cardiovascular Medicine March 2018

Cardiac Complications

- Different approaches have been used up front to decrease the long term risk
- Lipshultz et al. looked at continuous infusion of doxorubicin vs bolus infusion and it did not show a difference in long-term cardioprotection
- Use of dexrazoxane – iron-chelating agent
- Use of ACEIs as prevention and as treatment

Lipshultz SE et al. Pediatrics Vol 130 Nr 6 Dec 2012

Survivorship Guidelines

to determine indicated screening for individual patients.

Doxorubicin: Multiply total dose x 1

Daunorubicin: Multiply total dose x 0.5

Epirubicin: Multiply total dose x 0.67

Idarubicin: Multiply total dose x 5

Mitoxantrone: Multiply total dose x 4

ECHO (or comparable imaging to evaluate cardiac function)

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/m^2	< 15 Gy or none	Every 5 years
	≥ 15 Gy	Every 2 years
≥ 250 mg/m^2	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.

EKG (include evaluation of QTc interval)

Baseline at entry into long-term follow-up, repeat as clinically indicated

POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION

Cardiac MRI as an adjunct imaging modality when echocardiographic images are suboptimal.

Cardiology consultation in patients with subclinical abnormalities on screening evaluations, left ventricular dysfunction, dysrhythmia, or prolonged QTc interval.

Female patients only: For patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received:

- ≥250 mg/m^2 anthracyclines
- ≥35 Gy chest radiation, or
- Anthracycline (any dose) combined with chest radiation (≥15 Gy)

Evaluation should include a baseline echocardiogram (pre- or early-pregnancy). For those without prior abnormalities and with normal pre- or early-pregnancy baseline echocardiograms, follow-up echocardiograms may be obtained at the provider's discretion. Those with a history of systolic dysfunction or with pre- or early-pregnancy systolic dysfunction are at highest risk for pregnancy-associated cardiomyopathy. Such individuals should be monitored periodically during pregnancy and during labor and delivery due to increased risk for cardiac failure.

SYSTEM = Cardiovascular

SCORE = 1

COG, Long-Term Follow Up Guidelines for survivors of childhood, adolescent and young adult cancer, Oct 2018

Cardiac Complications

Table 1: Preliminary harmonized recommendations for surveillance of asymptomatic coronary artery disease in childhood, adolescent and young adult cancer survivors
General recommendation
Health care providers and childhood, adolescent and young adult cancer survivors treated with radiotherapy involving the heart should be aware of the increased risk of coronary artery disease (low level evidence and expert opinion, strong recommendation).
Who needs surveillance for asymptomatic CAD?
Surveillance of all childhood, adolescent and young adult cancer survivors for asymptomatic CAD is currently not recommended (no studies/expert opinion, strong recommendation)
What advice should be given regarding modifiable risk factors?
Surveillance for modifiable cardiovascular disease risk factors (i.e. overweight/obesity, hypertension, dyslipidemia, smoking, diabetes) is recommended with timing of initiation and frequency based on intensity of cardiotoxic treatment exposure(s), family history and presence of co-morbid conditions associated with CVD risk (low to moderate level evidence and expert opinion, strong recommendation).
Timely and aggressive management of modifiable cardiovascular disease risk factors (i.e. overweight/obesity, hypertension, dyslipidemia, smoking, diabetes) is reasonable due to the increased risk of coronary artery disease (existing guidelines and expert opinion, moderate recommendation).

Van Dalen et al. Coronary artery disease surveillance for childhood , adolescent and young adult cancer survivors-recommendations from the international guidelines harmonization group. Jun 2019 NASLCCC

Pulmonary Complications

- Caused by bleomycin, radiation therapy, BMT
- Types: germ cell tumors, lymphomas, BMT
- Can present with:
  - Pulmonary fibrosis
  - Decrease pulmonary function
  - Chronic GVHD
- Yearly physicals and evaluation with pulmonary function test as indicated
- Need for vaccination with Pneumococcal 23 vaccine and flu vaccine yearly
- Smoke avoidance, staying active

Ophthalmological Complications

- Caused by radiation therapy, steroids, BMT, tumor
- Types: leukemia, BMT, brain tumor, retinoblastoma, neuroblastoma
- Can present with:
  - Cataracts
  - Chronic GVHD
  - Blindness
- Need for every 1-2 years evaluations

Dental complications

- Caused by any chemotherapy, radiation therapy
- Young age at treatment <5yo
- Can present with:
  - Enamel dysplasia
  - Microdontia
  - Tooth agenesis
  - Mandibular problems
- Needs dental exam every 6 months and sometime oral rehabilitation with implants

Renal complications

- Caused by chemotherapy: alkylating agents – cyclophosphamide, ifosfamide, heavy metals - carboplatin and cisplatin, radiation therapy, BMT or surgery
- Types: sarcomas, neuroblastoma, renal tumors, brain tumors
- Can present with:
  - Hypertension
  - Glomerular injury
  - Renal insufficiency
- Annual screen with physical exam, blood pressure, laboratory tests
- Education about hydration, healthy habits

Secondary neoplasms

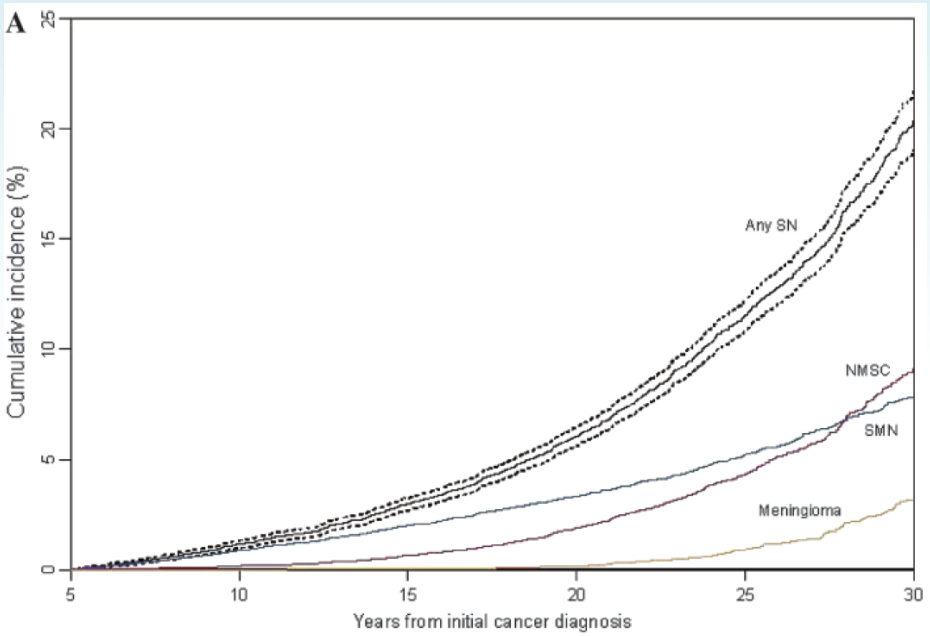
- Defined as histologically different second cancer that develops after the first cancer
- It can be in the same location or new location
- It can develop at any point in time
- Benign/malignant

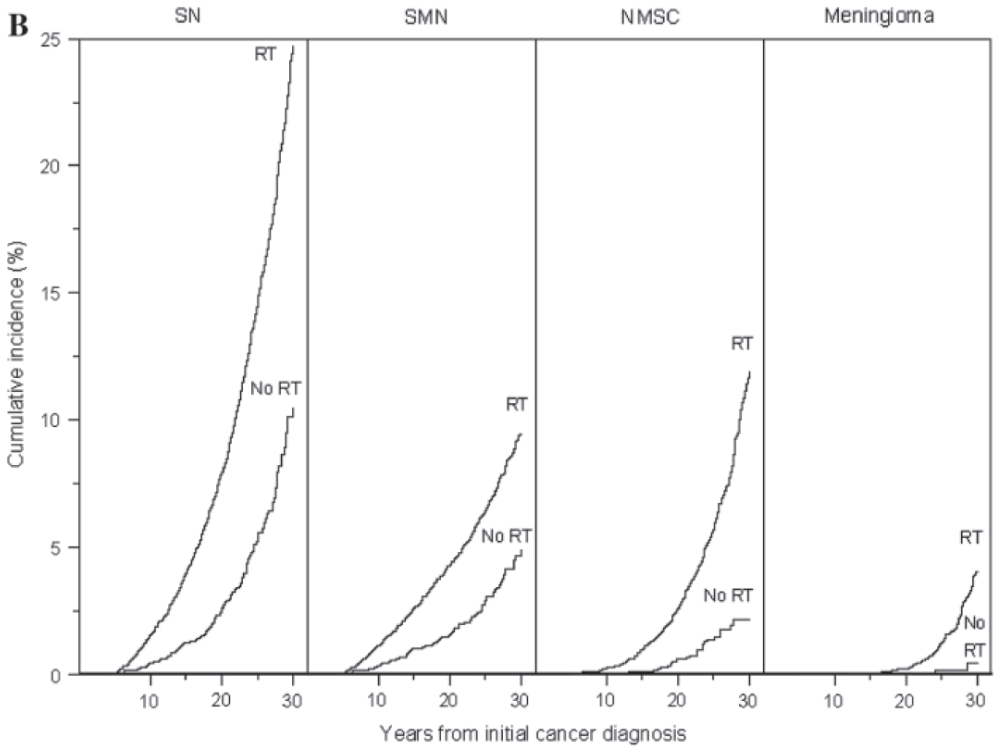
Secondary neoplasms

- Causes:
  - Patient-related causes: age, gender, smoking, genetics
  - Treatment-related causes: chemotherapy, radiation

- Underlying genetic predisposition like
  - Li Fraumeni
  - Neurofibromatosis
  - RB1 mutation – hereditary retinoblastoma
  - Fanconi Anemia

Cumulative incidence of second neoplasms (SNs) at 30 years after initial cancer diagnosis. A) All SNs. Cumulative incidence of any SN, nonmelanoma skin cancer (NMSC), second malignant neoplasm (SMN), and meningioma is shown. B) All SNs stratified by radiation therapy (RT) treatment or no RT.





Friedman et al. J Natl Cancer Inst 2010;102:1083–1095

Chemotherapy

- Most commonly associated with treatment-associated leukemia
- Chemotherapy: etoposide, alkylating agents, anthracyclines
- Used in treating numerous cancers: leukemia, lymphoma, solid tumors
- Can cause MDS or t-AML, but it can also present as ALL or lymphomas
- Increased risk in the first 10 years from exposure for etoposide and at any point in time with others
- Difficult to treat

Treatment-associated leukemia

- *2011, Nottage et al* looked at the CCSS cohort for the risk leukemia after treatment
- 43 out of 14 358 developed leukemia at more than 5 years from primary diagnosis
- Compare with general population, CCSS survivors had a 6-fold increased risk for developing leukemia
- The risk was highest between 5-10 years from primary diagnosis, around 15-fold increased risk
- Risk of AML at more than 15 years from primary diagnosis was 5-fold increase

Nottage et al. Blood 2011. 117(23): 6315-6318

Radiation therapy

- Skin neoplasms
- Brain neoplasms
- Thyroid neoplasms
- Breast neoplasms
- Lung neoplasms
- Colorectal carcinoma
- Bone neoplasms

Thyroid nodules

- Can be benign or malignant
- Risk factors: young age, female, location (head, neck, spine, TBI)
- Types: brain tumor, lymphomas, sarcomas
- Risk for thyroid cancer: dose (10-30Gy), alkylating agents, young age
- Examination is important and some advocate for US screening yearly after 10 years from treatment
- Need to be evaluated with US and possible FNA/ resection

Breast cancer

- Most common in female patients that have been treated with chest radiation therapy for Hodgkin's lymphoma
- Other patients that received chest or axilla radiation therapy, TBI
- Increase risk for patients with family history of breast cancer, increase dose, present of genetic mutations
- Yearly exam with beginning of puberty
- At 8 years off therapy or at age 25 which ever occurs last, it is recommended to have a mammography +/- breast MRI
- Important to have patient education for self exams

Lung cancer

- If you need another reason not to start smoking……
- Patients that receive chest, axilla or TBI and smoke are at higher risk to develop lung cancer
- Screening with annual exams for symptoms and physical examination
- Education of symptoms
- Smoking cessation
- New recommendation for spiral CT for smoking patients

Colorectal carcinoma

- Associated with abdominal radiation, pelvic radiation, spine radiation and TBI
- Family history of colorectal cancer or polyps
- Higher doses, combination with alkylating agents
- CCSS cohort – out of 802 secondary malignancy diagnosis, 27 were small intestine and colorectal cancer
- Recommended screening at 5 years off therapy or age 30 which ever occurs last
- Screening with stool DNA testing every 3 years and colonoscopy every 5 years

Surgical complications

- Limb amputation
- Enucleation
- Splenectomy
- Nephrectomy
- Orchiectomy
- Oophorectomy
- Lymphedema
- Graft failure
- Scars

Long term complications post transplant

- Associated with the prep regimen used
  - Renal toxicity
  - Skin toxicity
  - Pulmonary toxicity
  - Endocrinologic complications
  - Cardiac toxicity
  - Eye toxicity
- Graft versus host disease can occur up to 7 years post transplant
  - Acute
  - Chronic

Other complications

- Insurance
- Education/job
- Access to survivorship clinic or services

Newer therapies/changes

- Advances in leukemia from decreasing/excluding radiation therapy to introduction of new therapies like
    - CAR-T (chimeric antigen receptor T cells)
    - Targeted therapy (blinatumomab, Tyrosine Kinase Inhibitors-TKIs)

- Recommendations for bone marrow transplant

- Defining risk factors which influence therapy
    - Standard risk ALL – has a 95% survivor rate at 5 years with decrease in steroid use
    - Minimal residual disease (MRD)
    - Down syndrome patients with leukemia

Newer therapies/changes

- Advances in stage IV neuroblastoma with introduction of tandem autologous bone marrow transplants, antibody directed therapy and cis retinoic acid have increased survival to close to 70%

- Use of proton beam radiation for Hodgkin lymphoma, sarcoma, brain tumor that theoretically should reduce the long term side effects of radiation without interfering with survivor rate

- Using protective mechanism like dextrazaxone and thiosulfate

- Surgical approaches have changed over time like limb salvage surgery for osteosarcoma

Newer therapies/changes

- There is a lag between intro of a new therapy and late effects
- Very limited data in pediatric survivors
- Mostly is acute toxicity
- Some of the effects are starting to be described:
    - TKIs can affect height in prepubertal patients
    - Cis-retinoic acid can cause premature closing of growth plates
    - TKIs can cause hypothyroidism
- Studies in some areas are undergoing to look at these side effects long term

Conclusions

- Screening of cancer survivors for long term side effects is important
- With changes in therapies, there will be changes in survivorship follow-up
- Patient education is important
- Provider education is important
- Goal is to have functional adults that have good quality of life

References

- ***COG, Long-Term Follow Up Guidelines for survivors of childhood, adolescent and young adult cancer, Oct 2018;***
- ***Source: Surveillance, Epidemiology, and End Results (SEER) Program (seer.cancer.gov). SEER 9 area. Based on follow-up of patients into 2012;***
- ***Kenney LB, Melvin P, Fishman LN. Transition and transfer of childhood cancer survivors to adult care: A national survey of pediatric oncologists. Pediatric Blood Cancer, Jul 2016;***
- ***Kirch R et al. Advancing a Comprehensive Cancer Care Agenda for Children and Their Families: Institute of Medicine Workshop Highlights and Next Steps. CA, Oct 2016;***
- ***http://survivorshipguidelines.org/***

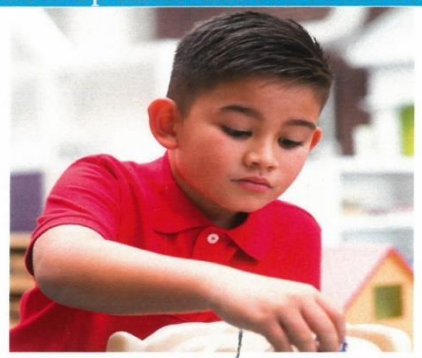
Thank you

We want to thank the patients and their families

Questions

Our clinic

F.A.C.T Clinic
(Follow-up After Cancer Treatment)



It's time to take the next step in your journey and transition to the F.A.C.T. Clinic!

Even though you are a cancer survivor, it is still important that you continue to have regular medical care. Our F.A.C.T. program offers cancer survivors the opportunity to continue follow-up care based on the latest recommendations from the Children's Oncology Group (COG). Our goal is to recognize and help minimize side effects related to your cancer treatment. We typically see patients once a year but we encourage you to call our coordinator if questions or concerns arise.

musc Children's Health
Medical University of South Carolina

Changing What's Possible

What to Expect

A thorough physical exam and evaluation from one of our highly qualified medical professionals.

A comprehensive review of your cancer treatment whether you were treated at MUSC or an outside facility.

Completion of blood work specific to your cancer history. Results will be reviewed with you in clinic that day.

Same day testing, based on your treatment history, may include an echocardiogram, pulmonary function test, bone density scans, ultrasounds, chest x-rays or EKGs.

Coordination of appointments with other needed medical services on the day of your FACT visit.

F.A.C.T. Healthcare Providers

Anca Dumitriu MD

FACT Coordinator: Sheri Fannin RN, BSN, CCRN

Social Worker: Tiombe Plair LMSW

Child Life Specialist: Michelle Vandermaas

F.A.C.T. Location

Summey Medical Pavilion

F.A.C.T. Dates/Times

FACT Clinic appointments are scheduled in the morning on the 1st and 3rd Thursday of every month, pending holiday schedules.

musc Children's Health
Medical University of South Carolina

Changing What's Possible

MUSCkids.org CHILDREN'S ONCOLOGY GROUP The world's childhood cancer experts 843-792-7194

- Start when patients are at least 2 years off active therapy or 5 years from diagnosis
- We see up to age 25-30 yo
- Goal is to educate patients to be able to advocate for themselves
- Also, to educate families and other providers of survivors medical needs